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(54) INGESTION OF HYALURONIC ACID FOR IMPROVED JOINT FUNCTION AND HEALTH

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(57) ABSTRACT

A method is described for relieving joint pain and discomfort in a warm-blooded vertebrate by delivering via oral ingestion a nutritional supplement comprising an effective amount of hyaluronic acid, or a salt or digest thereof, and a nutritionally acceptable carrier. In another embodiment of the present invention, a method is provided for reducing the discomfort of fibromyalgia in a person afflicted with fibromyalgia by delivering via oral ingestion a nutritional supplement comprising an effective amount of hyaluronic acid, or a salt or digest thereof, and a nutritionally acceptable carrier.

INGESTION OF HYALURONIC ACID FOR IMPROVED JOINT FUNCTION AND HEALTH

FIELD OF THE INVENTION

[0001] The present invention relates to a method for relieving joint pain or other discomfort in a warm-blooded vertebrate. More particularly, this invention provides relief of symptoms of arthritic disorders or fibromyalgia by oral ingestion of a composition comprising an effective amount of hyaluronic acid, or a salt or digest thereof.

BACKGROUND AND SUMMARY OF THE INVENTION

[0002] Arthritic disorders, including acute and chronic rheumatoid arthritis and osteoarthritis as well as inflammatory skeletal and musculoskeletal conditions, affect millions of people. It has been estimated that 80% of all individuals over the age of 55 suffer from some form of arthritic disorder. The most common arthritic disorder is osteoarthritis. Osteoarthritis develops gradually over time in many cases. Patients experience alternating periods of mild to moderate pain, stiffness, and swelling of the joint and periods of relatively symptom-free joint activity. Osteoarthritis is characterized by the deterioration of cartilage that covers the ends of bones at a joint, such as the knee or hip. In the healthy joint, cartilage acts as a shock absorber and aids the joint in bearing the stress of physical movement. In addition, synovial joint fluid produced by the synovial membrane lubricates the joint providing a slippery surface over which the bones may move. But as cartilage deteriorates, the bones begin to rub against each other causing joint pain.

[0003] At the same time, the concentration of hyaluronic acid in the synovial joint decreases, reducing the lubrication ability of the synovial joint fluid. Also, joint movement may be restricted as bone ends erode or thicken, and the bones may develop painful outgrowths, or bone spurs, as a result of this erosion or thickening. If left untreated, cartilage deterioration can seriously weaken the joint, possibly to the point of deformity.

[0004] Current methods of reducing pain in osteoarthritic joints include treatment with analgesics or anti-inflammatory medications, physical therapy, topical application of hyaluronic acid to the joint, and intra-articular injection of hyaluronic acid directly into the joint. The primary goal of treatment is reduction of pain and maintenance of joint function and strength. Intra-articular injections of hyaluronic acid, known as viscosupplementation, have seen wide use for patients who have not responded well to other therapies.

[0005] Fibromyalgia is a common disabling disorder characterized by chronic musculoskeletal aches and pain, stiffness, general fatigue, and sleep abnormalities. The disorder affects 2-4% of the population and is most frequently found in women between 20 and 50 years old. The exact cause of fibromyalgia remains uncertain, and diagnosis is difficult due to the general nature of the symptoms. Currently, the most effective treatment for fibromyalgia includes a combination of analgesics, sleep aids, exercise programs, relaxation techniques and other measures to reduce muscle tension. These treatments are geared toward improving sleep quality and reducing pain.

[0006] The present invention is directed to a method for relieving joint and musculoskeletal discomfort in warm-blooded vertebrates comprising the step of delivering to the vertebrate by oral ingestion a composition comprising an effective amount of hyaluronic acid, or a salt or digest thereof, and an acceptable ingestible carrier. The method is used with advantage in treating conditions associated with osteoarthritis and for reducing the discomfort of fibromyalgia in a person afflicted with fibromyalgia.

DETAILED DESCRIPTION OF THE INVENTION

[0007] Hyaluronic acid is a mucopolysaccharide that is found in joint tissue and in the vitreous humor of the eye. Hyaluronic acid functions as a protective coating and a lubricant for soft tissue and joints, and additionally, helps maintain the structural integrity of soft tissue. In association with protein, hyaluronic acid binds water in the intercellular spaces and holds cells together in a jellylike matrix. This jellylike matrix provides lubrication and shock absorption throughout the body.

[0008] In the healthy knee joint, hyaluronic acid is present both in the cartilage covering the ends of bone and in the synovial joint fluid. Hyaluronic acid is usually found as part of proteoglycan aggregates in cartilage, where it helps cartilage withstand forces of weight bearing and joint movement. Hyaluronic acid is also a major component of synovial joint fluid. The synovial joint fluid provides lubrication for the cartilage against the lining of the joint and may provide some additional shock-absorption value.

[0009] Hyaluronic acid is commercially available and is prepared from the intracellular matrices of animal connective tissue, such as rooster combs and bovine tissue sources, mammalian umbilical cords, and bacterial organisms such as streptococcus zoepidicus. Its molecular weight ranges from about 50000 to about 8×10^6 Daltons depending on source and method of isolation. Treatment with hyaluronidases can be used to provide hydrolysates of reduced molecular weight range.

[0010] The present method provides relief from joint pain and musculoskeletal discomfort in a warm-blooded vertebrate suffering from an arthritic condition or fibromyalgia. An arthritic condition includes acute and chronic rheumatoid arthritis and osteoarthritis, as well as inflammatory conditions involving skeletal conditions and musculoskeletal conditions.

[0011] In accordance with the present invention, a method is provided for relieving joint or musculoskeletal pain or discomfort in a warm-blooded vertebrate comprising delivering to the vertebrate by oral ingestion a composition comprising an effective amount of hyaluronic acid, or a salt or digest thereof, and a nutritionally acceptable carrier. An "effective amount" as used herein refers to the amount of hyaluronic acid which, upon oral administration, provides relief of joint pain or discomfort. The effective amount of hyaluronic acid, or a salt or digest thereof, is from about 0.1 μg/kg to about 400 μg/kg of body weight per dose. The warm-blooded vertebrate may be a human, or an equine, canine, or feline species. In one embodiment the method is used to reduce joint pain n a person afflicted with osteoarthritis.

[0012] In another embodiment the method is used for reducing the discomfort of fibromyalgia. The hyaluronic acid, salt or digest is orally ingested with a acceptable carrier, typically an aqueous beverage or food product. Preferably, the hyaluronic acid, salts or hydrolysates for use in the present invention is formulated into a liquid aqueous concentration, for example, a dietary supplement formulation, which is diluted in portions and mixed with food, water, or other beverages for oral ingestion. Alternatively the hyaluronic acid, salt, or hydrolysate can be packaged in individual solid or liquid doses, for instance in capsules or gel seals. The concentrate can contain about 1 to about 10 mg of hyaluronic acid, its salt or hydrolysate per milliliter of concentrate. In one embodiment a dose is administered by combining 7 to 10 drops of the concentrate in a cold beverage which is consumed on conjunction with a meal, for example.

EXAMPLES

Example 1

Oral Ingestion of Hyaluronic Acid By Patients Suffering From Osteoarthritis

[0013] A study involving sixty-seven patients suffering from osteoarthritis was undertaken to determine the effectiveness of oral ingestion of hyaluronic acid. Each patient received 1-4 mg of hyaluronic acid by oral ingestion administration 1 to 4 times a day over periods ranging from about 4 to about 2 weeks, during which period the patients' subjective pain feeling was reported. Twenty-nine patients (43.3%) reported no pain after oral ingestion of hyaluronic acid, and additionally reported increased range of motion. Twenty-four patients reported (35.8%) some degree of pain relief and some increased range of motion. Fourteen patients reported no change in the amount of pain they felt.

Example 2

Oral Ingestion of Hyaluronic Acid by Patients Afflicted With Fibromyalgia

[0014] Another study involving thirty-five human patients suffering pain and discomfort associated with fibromyalgia was undertaken to evaluate the effectiveness of oral ingestion of hyaluronic acid. Each patient received about 1 to about 6 mg of hyaluronic acid by oral ingestion administration of concentrate diluted into beverages or food. Over a treatment period of about 1 to about 14 months, the patients' subjective pain feeling was reported. Twenty-one patients reported no pain after hyaluronic acid therapy. Six patients (17.1%) reported some (60%) degree of pain relief. Eight patients reported no change in the amount of pain they felt.

1. A method for relieving joint pain or other discomfort in a warm-blooded vertebrate comprising the step of delivering to said vertebrate by oral ingestion a composition comprising an effective amount of hyaluronic acid, or a salt or digest thereof, and a food acceptable carrier.

2. The method of claim 1 wherein the nutritional supplement consists essentially of said hyaluronic acid, or a salt or digest thereof, and the carrier therefor.

3. The method of claim 1 further comprising the step of adding the hyaluronic acid, or a salt or digest thereof, to the carrier, and wherein the carrier comprises food or water.

4. The method of claim 1 wherein the nutritional supplement is provided in capsule form.

5. The method of claim 1 wherein the effective amount of hyaluronic acid, or a salt or digest thereof, is from about 0.1 μg to about 400 μg/kg of body weight.

6. The method of claim 1 wherein the warm-blooded vertebrate is a human, or an equine, canine, or feline species.

7. The method of claim 1 wherein the joint pain is the result of an arthritic condition.

8. The method of claim 1 wherein the joint pain is the result of an inflammatory condition involving skeletal or musculoskeletal structures.

9. A method for reducing discomfort of fibromyalgia in a person afflicted with fibromyalgia comprising the step of delivering to said person by oral ingestion a nutritional supplement comprising an effective amount of hyaluronic acid, or a salt or digest thereof, and a nutritionally acceptable carrier.

10. The method of claim 9 wherein the nutritional supplement consists essentially of said hyaluronic acid, or a salt or digest thereof, and the carrier therefor.

11. The method of claim 9 further comprising the step of adding the hyaluronic acid, or a salt or digest thereof, to the carrier, and wherein the carrier comprises food or water.

12. The method of claim 9 wherein the nutritional supplement is provided in capsule form.

13. The method of claim 9 wherein the effective amount of hyaluronic acid, or a salt or digest thereof, is from about 0.1 μg to about 400 μg/kg of body weight.

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(54) **INGESTION OF HYALURONIC ACID FOR IMPROVED JOINT FUNCTION AND HEALTH**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/860,425**

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(58) **Field of Search** 424/400, 439, 424/442, 451, 452; 514/825

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(57) **ABSTRACT**

Methods are described for relieving discomforts associated with osteoarthritis or fibromyalgia. The methods comprise the step of delivering by oral ingestion a nutritional supplement consisting essentially of an effective amount of hyaluronic acid, or a salt or digest thereof, and a food acceptable carrier, wherein the effective amount of hyaluronic acid, or a salt or digest thereof, is from about 0.1 μg to about 400 μg/kg of body weight.

7 Claims, No Drawings

INGESTION OF HYALURONIC ACID FOR IMPROVED JOINT FUNCTION AND HEALTH

FIELD OF THE INVENTION

The present invention relates to a method for relieving joint pain or other discomfort in a warm-blooded vertebrate. More particularly, this invention provides relief of symptoms of arthritic disorders or fibromyalgia by oral ingestion of a composition comprising an effective amount of hyaluronic acid, or a salt or digest thereof.

BACKGROUND AND SUMMARY OF THE INVENTION

Arthritic disorders, including acute and chronic rheumatoid arthritis and osteoarthritis as well as inflammatory skeletal and musculoskeletal conditions, affect millions of people. It has been estimated that 80% of all individuals over the age of 55 suffer from some form of arthritic disorder. The most common arthritic disorder is osteoarthritis. Osteoarthritis develops gradually over time in many cases. Patients experience alternating periods of mild to moderate pain, stiffness, and swelling of the joint and periods of relatively symptom-free joint activity. Osteoarthritis is characterized by the deterioration of cartilage that covers the ends of bones at a joint, such as the knee or hip. In the healthy joint, cartilage acts as a shock absorber and aids the joint in bearing the stress of physical movement. In addition, synovial joint fluid produced by the synovial membrane lubricates the joint providing a slippery surface over which the bones may move. But as cartilage deteriorates, the bones begin to rub against each other causing joint pain.

At the same time, the concentration of hyaluronic acid in the synovial joint decreases, reducing the lubrication ability of the synovial joint fluid. Also, joint movement may be restricted as bone ends erode or thicken, and the bones may develop painful outgrowths, or bone spurs, as a result of this erosion or thickening. If left untreated, cartilage deterioration can seriously weaken the joint, possibly to the point of deformity.

Current methods of reducing pain in osteoarthritic joints include treatment with analgesics or anti-inflammatory medications, physical therapy, topical application of hyaluronic acid to the joint, and intra-articular injection of hyaluronic acid directly into the joint. The primary goal of treatment is reduction of pain and maintenance of joint function and strength. Intra-articular injections of hyaluronic acid, known as viscosupplementation, have seen wide use for patients who have not responded well to other therapies.

Fibromyalgia is a common disabling disorder characterized by chronic musculoskeletal aches and pain, stiffness, general fatigue, and sleep abnormalities. The disorder affects 2–4% of the population and is most frequently found in women between 20 and 50 years old. The exact cause of fibromyalgia remains uncertain, and diagnosis is difficult due to the general nature of the symptoms. Currently, the most effective treatment for fibromyalgia includes a combination of analgesics, sleep aids, exercise programs, relaxation techniques and other measures to reduce muscle tension. These treatments are geared toward improving sleep quality and reducing pain.

The present invention is directed to a method for relieving joint and musculoskeletal discomfort in warm-blooded vertebrates comprising the step of delivering to the vertebrate by oral ingestion a composition comprising an effective amount of hyaluronic acid, or a salt or digest thereof, and an acceptable ingestible carrier. The method is used with advantage in treating conditions associated with osteoarthritis and for reducing the discomfort of fibromyalgia in a person afflicted with fibromyalgia.

DETAILED DESCRIPTION OF THE INVENTION

Hyaluronic acid is a mucopolysaccharide that is found in joint tissue and in the vitreous humor of the eye. Hyaluronic acid functions as a protective coating and a lubricant for soft tissue and joints, and additionally, helps maintain the structural integrity of soft tissue. In association with protein, hyaluronic acid binds water in the intercellular spaces and holds cells together in a jellylike matrix. This jellylike matrix provides lubrication and shock absorption throughout the body.

In the healthy knee joint, hyaluronic acid is present both in the cartilage covering the ends of bone and in the synovial joint fluid. Hyaluronic acid is usually found as part of proteoglycan aggregates in cartilage, where it helps cartilage withstand forces of weight bearing and joint movement. Hyaluronic acid is also a major component of synovial joint fluid. The synovial joint fluid provides lubrication for the cartilage against the lining of the joint and may provide some additional shock-absorption value.

Hyaluronic acid is commercially available and is prepared from the intracellular matrices of animal connective tissue, such as rooster combs and bovine tissue sources, mammalian umbilical cords, and bacterial organisms such as streptococcus zoepidicus. Its molecular weight ranges from about 50000 to about 8×10^6 Daltons depending on source and method of isolation. Treatment with hyaluronidases can be used to provide hydrolysates of reduced molecular weight range.

The present method provides relief from joint pain and musculoskeletal discomfort in a warm-blooded vertebrate suffering from an arthritic condition or fibromyalgia. An arthritic condition includes acute and chronic rheumatoid arthritis and osteoarthritis, as well as inflammatory conditions involving skeletal conditions and musculoskeletal conditions.

In accordance with the present invention, a method is provided for relieving joint or musculoskeletal pain or discomfort in a warm-blooded vertebrate comprising delivering to the vertebrate by oral ingestion a composition comprising an effective amount of hyaluronic acid, or a salt or digest thereof, and a nutritionally acceptable carrier. An "effective amount" as used herein refers to the amount of hyaluronic acid which, upon oral administration, provides relief of joint pain or discomfort. The effective amount of hyaluronic acid, or a salt or digest thereof, is from about 0.1 μg/kg to about 400 μg/kg of body weight per dose. The warm-blooded vertebrate may be a human, or an equine, canine, or feline species. In one embodiment the method is used to reduce joint pain n a person afflicted with osteoarthritis.

In another embodiment the method is used for reducing the discomfort of fibromyalgia. The hyaluronic acid, salt or digest is orally ingested with a acceptable carrier, typically an aqueous beverage or food product. Preferably, the hyaluronic acid, salts or hydrolysates for use in the present invention is formulated into a liquid aqueous concentration, for example, a dietary supplement formulation, which is diluted in portions and mixed with food, water, or other beverages for oral ingestion. Alternatively the hyaluronic

acid, salt, or hydrolysate can be packaged in individual solid or liquid doses, for instance in capsules or gel seals. The concentrate can contain about 1 to about 10 mg of hyaluronic acid, its salt or hydrolysate per milliliter of concentrate. In one embodiment a dose is administered by combining 7 to 10 drops of the concentrate in a cold beverage which is consumed on conjunction with a meal, for example.

EXAMPLES

Example 1

Oral Ingestion of Hyaluronic Acid By Patients Suffering From Osteoarthritis

A study involving sixty-seven patients suffering from osteoarthritis was undertaken to determine the effectiveness of oral ingestion of hyaluronic acid. Each patient received 1–4 mg of hyaluronic acid by oral ingestion administration 1 to 4 times a day over periods ranging from about 4 to about 2 weeks, during which period the patients' subjective pain feeling was reported. Twenty-nine patients (43.3%) reported no pain after oral ingestion of hyaluronic acid, and additionally reported increased range of motion. Twenty-four patients reported (35.8%) some degree of pain relief and some increased range of motion. Fourteen patients reported no change in the amount of pain they felt.

Example 2

Oral Ingestion of Hyaluronic Acid by Patients Afflicted With Fibromyalgia

Another study involving thirty-five human patients suffering pain and discomfort associated with fibromyalgia was undertaken to evaluate the effectiveness of oral ingestion of hyaluronic acid. Each patient received about 1 to about 6 mg of hyaluronic acid by oral ingestion administration of concentrate diluted into beverages or food. Over a treatment period of about 1 to about 14 months, the patients' subjective pain feeling was reported. Twenty-one patients reported no pain after hyaluronic acid therapy. Six patients (17.1%) reported some (60%) degree of pain relief. Eight patients reported no change in the amount of pain they felt.

What is claimed is:

1. A method for relieving joint pain or other discomforts associated with osteoarthritis in a warm-blooded vertebrate comprising the step of delivering to said vertebrate by oral ingestion a nutritional supplement consisting essentially of an effective amount of hyaluronic acid, or a salt or digest thereof, and a food acceptable carrier, wherein the effective amount of hyaluronic acid, or a salt or digest thereof, is from about 0.1 μg to about 400 μg/kg of body weight.

2. The method of claim **1** further comprising the step of adding the hyaluronic acid, or a salt or digest thereof, to the carrier, and wherein the carrier comprises food or water.

3. The method of claim **1** wherein the nutritional supplement is provided in capsule form.

4. The method of claim **1** wherein the warm-blooded vertebrate is a human, or an equine, canine, or feline species.

5. A method for reducing discomfort of fibromyalgia in a person afflicted with fibromyalgia comprising the step of delivering to said person by oral ingestion a nutritional supplement consisting essentially of an effective amount of hyaluronic acid, or a salt or digest thereof, and a nutritionally acceptable carrier, wherein the effective amount of hyaluronic acid, or a salt or digest thereof, is from about 0.1 μg to about 400 μg/kg of body weight.

6. The method of claim **5** further comprising the step of adding the hyaluronic acid, or a salt or digest thereof, to the carrier, and wherein the carrier comprises food or water.

7. The method of claim **5** wherein the nutritional supplement is provided in capsule form.

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(54) **INGESTION OF HYALURONIC ACID FOR IMPROVED JOINT HEALTH**

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(21) Appl. No.: **10/629,880**

(22) Filed: **Jul. 29, 2003**

Related U.S. Application Data

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Publication Classification

(51) **Int. Cl.**[7] **A61K 31/728**; A61K 9/48

(52) **U.S. Cl.** **424/452**; 514/54; 424/442

(57) **ABSTRACT**

Methods and compositions are described for relieving joint pain and discomfort in a warm-blooded vertebrate by delivering via oral ingestion a nutritional supplement comprising an effective amount of hyaluronic acid, or a salt or digest thereof, and a nutritionally acceptable carrier.

INGESTION OF HYALURONIC ACID FOR IMPROVED JOINT HEALTH

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 09/860,425, filed May 18, 2001, herein incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to a method for relieving joint pain or other discomfort in a warm-blooded vertebrate. More particularly, this invention provides relief of symptoms of arthritic disorders or fibromyalgia by oral ingestion of a composition comprising an effective amount of hyaluronic acid, or a salt or digest thereof.

BACKGROUND AND SUMMARY OF THE INVENTION

[0003] Arthritic disorders, including acute and chronic rheumatoid arthritis and osteoarthritis as well as inflammatory skeletal and musculoskeletal conditions, affect millions of people. It has been estimated that 80% of all individuals over the age of 55 suffer from some form of arthritic disorder. The most common arthritic disorder is osteoarthritis. Osteoarthritis develops gradually over time in many cases. Patients experience alternating periods of mild to moderate pain, stiffness, and swelling of the joint and periods of relatively symptom-free joint activity.

[0004] Osteoarthritis is characterized by the deterioration of cartilage that covers the ends of bones at a joint, such as the knee or hip. In the healthy joint, cartilage acts as a shock absorber and aids the joint in bearing the stress of physical movement. In addition, synovial joint fluid produced by the synovial membrane lubricates the joint providing a slippery surface over which the bones may move. But as cartilage deteriorates, the bones begin to rub against each other causing joint pain. At the same time, the concentration of hyaluronic acid in the synovial joint decreases, reducing the lubrication ability of the synovial joint fluid. Also, joint movement may be restricted as bone ends erode or thicken, and the bones may develop painful outgrowths, or bone spurs, as a result of this erosion or thickening. If left untreated, cartilage deterioration can seriously weaken the joint, possibly to the point of deformity.

[0005] Current methods of reducing pain in osteoarthritic joints include treatment with analgesics or anti-inflammatory medications, physical therapy, topical application of hyaluronic acid to the joint, and intra-articular injection of hyaluronic acid directly into the joint. The primary goal of treatment is reduction of pain and maintenance of joint function and strength. Intra-articular injections of hyaluronic acid, known as viscosupplementation, have seen wide use for patients who have not responded well to other therapies.

[0006] Fibromyalgia is a common disabling disorder characterized by chronic musculoskeletal aches and pain, stiffness, general fatigue, and sleep abnormalities. The disorder affects 2-4% of the population and is most frequently found in women between 20 and 50 years old. The exact cause of fibromyalgia remains uncertain, and diagnosis is difficult due to the general nature of the symptoms. Currently, the most effective treatment for fibromyalgia includes a combination of analgesics, sleep aids, exercise programs, relaxation techniques and other measures to reduce muscle tension. These treatments are geared toward improving sleep quality and reducing pain.

[0007] Rheumatoid Arthritis is a chronic, systemic, inflammatory disease that chiefly affects the synovial membranes of multiple joints in the body. Rheumatoid arthritis is considered to be an autoimmune disease, in which the patient has remissions and exacerbations of the symptoms. Joints that are actively involved with the disease are usually tender, swollen, and likely demonstrate reduced motion. Several different classes of drugs are often use to treat patients with rheumatoid arthritis, including analgesics to control pain, corticosteroids, uric acid-lowering drugs, immunosuppressive drugs, nonsteroidal antiinflammatory drugs, and disease-modifying antirheumatic drugs. Many patients with rheumatoid arthritis also note a decrease in their symptoms after application of heat.

[0008] The present invention is directed to a method for relieving joint and musculoskeletal discomfort in warm-blooded vertebrates comprising the step of delivering to the vertebrate by oral ingestion a composition comprising an effective amount of hyaluronic acid, or a salt or digest thereof, and an acceptable ingestible carrier. The method is used with advantage in treating conditions associated with arthritis and for reducing the discomfort of fibromyalgia in a person afflicted with fibromyalgia.

[0009] Additional features of the present invention will become apparent to those skilled in the art upon consideration of the following detailed description of the preferred embodiments.

DETAILED DESCRIPTION OF THE INVENTION

[0010] Hyaluronic acid is a mucopolysaccharide that is found in joint tissue and in the vitreous humor of the eye. Hyaluronic acid functions as a protective coating and a lubricant for soft tissue and joints, and additionally, helps maintain the structural integrity of soft tissue. In association with protein, hyaluronic acid binds water in the intercellular spaces and holds cells together in a jelly like matrix. This jellylike matrix provides lubrication and shock absorption throughout the body.

[0011] In the healthy knee joint, hyaluronic acid is present both in the cartilage covering the ends of bone and in the synovial joint fluid. Hyaluronic acid is usually found as part of proteoglycan aggregates in cartilage, where it helps cartilage withstand forces of weight bearing and joint movement. Hyaluronic acid is also a major component of synovial joint fluid. The synovial joint fluid provides lubrication for the cartilage against the lining of the joint and may provide some additional shock-absorption value.

[0012] Hyaluronic acid is commercially available and is prepared from the intracellular matrices of animal connective tissue, such as rooster combs and bovine tissue sources, mammalian umbilical cords, and bacterial organisms such as streptococcus zoepidicus. Its molecular weight ranges from about 50000 to about 8×10^6 Daltons depending on source and method of isolation. Treatment with hyaluronidases can be used to provide hydrolysates of reduced molecular weight range.

[0013] The present method provides relief from joint pain and musculoskeletal discomfort in a warm-blooded vertebrate suffering from an arthritic condition or fibromyalgia. An arthritic condition includes acute and chronic rheumatoid arthritis and osteoarthritis, as well as inflammatory conditions involving skeletal conditions and musculoskeletal conditions.

[0014] In accordance with the present invention, a method is provided for relieving joint or musculoskeletal pain or discomfort in a warm-blooded vertebrate comprising delivering to the vertebrate by oral ingestion a composition comprising an effective amount of hyaluronic acid, or a salt or digest thereof, and a nutritionally acceptable carrier. An "effective amount" as used herein refers to the amount of hyaluronic acid which, upon oral administration, provides relief of joint pain or discomfort. The effective amount of hyaluronic acid, or a salt or digest thereof, is from about 0.1 μg/kg to about 400 μg/kg of body weight per dose. The warm-blooded vertebrate may be a human, or an equine, canine, or feline species. In one embodiment the method is used to reduce joint pain in a person afflicted with osteoarthritis.

[0015] In another embodiment the method is used for reducing the discomfort of fibromyalgia. The hyaluronic acid, salt or digest is orally ingested with an acceptable carrier, typically an aqueous beverage or food product. Preferably, the hyaluronic acid, salts, or hydrolysates for use in the present invention are formulated into a liquid aqueous concentration, for example, a dietary supplement formulation, which is diluted in portions and mixed with food, water, or other beverages for oral ingestion. Alternatively the hyaluronic acid, salt, or hydrolysate can be packaged in individual solid or liquid doses, for instance in capsules or gel seals. The concentrate can contain about 1 to about 10 mg of hyaluronic acid, its salt, or hydrolysate per milliliter of concentrate. In one embodiment a dose is administered by combining 7 to 10 drops of the concentrate in a cold beverage which is consumed on conjunction with a meal, for example.

EXAMPLES

Example 1

Oral Ingestion of Hyaluronic Acid by Patients Suffering from Osteoarthritis

[0016] A study involving sixty-seven patients suffering from osteoarthritis was undertaken to determine the effectiveness of oral ingestion of hyaluronic acid. Each patient received 1-4 mg of hyaluronic acid by oral ingestion administration 1 to 4 times a day over periods ranging from about 4 to about 2 weeks, during which period the patients' subjective pain feeling was reported. Twenty-nine patients (43.3%) reported no pain after oral ingestion of hyaluronic acid, and additionally reported increased range of motion. Twenty-four patients reported (35.8%) some degree of pain relief and some increased range of motion. Fourteen patients reported no change in the amount of pain they felt.

Example 2

Oral Ingestion of Hyaluronic Acid by Patients Afflicted with Fibromyalgia

[0017] Another study involving thirty-five human patients suffering pain and discomfort associated with fibromyalgia was undertaken to evaluate the effectiveness of oral ingestion of hyaluronic acid. Each patient received about 1 to about 6 mg of hyaluronic acid by oral ingestion administration of concentrate diluted into beverages or food. Over a treatment period of about 1 to about 14 months, the patients' subjective pain feeling was reported. Twenty-one patients reported no pain after hyaluronic acid therapy. Six patients (17.1%) reported some (60%) degree of pain relief. Eight patients reported no change in the amount of pain they felt.

Example 3

Oral Ingestion of Hyaluronic Acid by Patients Afflicted with Rheumatoid Arthritis

[0018] Another study involving seventeen human patients suffering pain and discomfort associated with rheumatoid arthritis was undertaken. Each patient received about 1 mg of an oral hyaluronic acid solution for a period of 30 days. Each patient was asked to evaluate his or her subjective pain feeling and report the score on a scale of 0 to 10, wherein 0 means no pain and/or stiffness whatsoever and 10 means worst imaginable pain and/or stiffness. Prior to the start of the study, the patients reported as follows:

1 patient reported	7
8 patients reported	8
4 patients reported	9
2 patients reported	10

[0019] for an average of 8.47. At the completion of the 30-day study, the patients responded as follows:

1 patient reported	0
1 patient reported	1
3 patients reported	2
7 patients reported	3
2 patients reported	7
1 patient reposted	10

[0020] for an average of 3.47, which is considerably lower than the pain reported prior to treatment. Two of the seventeen patients did not respond to the questionnaire.

[0021] Given that oral ingestion of hyaluronic acid reduced join pain and other discomforts due to osteoarthritis, fibromyalgia, and rheumatoid arthritis, it is expected that oral ingestion of hyaluronic acid would reduce joint pain and stiffness resulting from a variety of conditions.

[0022] Although the invention has been described in detail with reference to certain preferred embodiments, those skilled in the art will recognize that the invention can be practiced with variations and modifications within the scope and spirit of the invention as described and defined in the following claims.

1. A method for relieving joint pain or other discomforts associated with joint disorders in a warm-blooded vertebrate comprising the step of delivering to said vertebrate by oral ingestion a nutritional supplement consisting essentially of an effective amount of hyaluronic acid, or a salt or digest thereof, and a food acceptable carrier, wherein the effective

amount of hyaluronic acid, or a salt or digest thereof, is from about 0.1 μg to about 400 μg/kg of body weight

2. The method of claim 1 further comprising the step of adding the hyaluronic acid, or a salt or digest thereof, to the carrier, and wherein the carrier comprises food or water.

3. The method of claim 1 wherein the nutritional supplement is provided in capsule form.

4. The method of claim 1 wherein the warm-blooded vertebrate is a human, or an equine, canine, or feline species.

5. The method of claim 1 wherein the joint pain is the result of an arthritic condition.

6. The method of claim 5 wherein the arthritic condition is selected from the group consisting of osteoarthritis and rheumatoid arthritis.

7. The method of claim 1 wherein the joint pain is the result of an inflammatory condition involving skeletal or musculoskeletal structures.

8. A nutritional supplement consisting essentially of an effective amount of hyaluronic acid, or a salt or digest thereof, and a food acceptable carrier, the nutritional supplement provided in an orally ingestible dosage form.

9. The nutritional supplement of claim 8 wherein the effective amount of hyaluronic acid is 1 to 6 mg.

10. The nutritional supplement of claim 8 wherein the orally ingestible dosage form is a capsule or gel seal.

* * * * *

10-04-00 A PROV

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 C.F.R. § 1.53(b)(2).

Attorney Docket Number: 2781.01US01

INVENTOR(S) / APPLICANT(S)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (City and Either State or Foreign Country)
Pierce	Scott		Lexington, Kentucky

TITLE OF INVENTION (280 characters max)

CHONDROPROTECTIVE/RESTORATIVE
COMPOSITIONS AND METHODS THEREOF

CORRESPONDENCE ADDRESS

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ENCLOSED APPLICATION PARTS (check all that apply)

[X]	Specification	Number of Pages: 37	[ ]	Small Entity Statement	
[X]	Drawings	Number of Sheets:	[ ]		

METHOD OF PAYMENT

[ ] A check in the amount of $0.00 is enclosed to cover the provisional application filing fee. The Commissioner is hereby authorized to charge any additional filing fees and/or to credit any overpayment to our Deposit Account Number 16-0631.

The invention was made by an agency of the U.S. Government or under a contract with an agency of the U.S. Government.

[X] No. [ ] Yes. The name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

Date: October 3, 2000

John F. Dolan
Registration. No. 45,382

PROVISIONAL APPLICATION FILING ONLY

CERTIFICATE OF EXPRESS MAIL

"Express Mail" mailing label number: EL595680945US. Date of Deposit: October 3, 2000. I hereby certify that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Jeanne Truman
Name of Person Making Deposit

Jeanne Truman
Signature

CHONDROPROTECTIVE/RESTORATIVE COMPOSITIONS AND METHODS THEREOF

Provisional Application

BACKGROUND OF THE INVENTION

The present invention, which goes by the name Chondrogen EQ, was initially formulated for the growing horse and equine athlete. It is the most unique chondroprotective / restorative agent available. In one embodiment, the molasses flavored oral paste provides a practical, efficient, and effective means of administration orally or top dressing feed. When added to the feed, this embodiments molasses base binds to the feed to insure total consumption. When necessary, an easy measure dose can be administered orally. This highly palatable formulation is the first to combine high levels of Glucosamine sulfate (GS) with Chondroitin sulfate (CS) and Hyaluronic Acid (HA) in an easy to absorb, low molecular weight formula. It has also been shown that liquid or paste forms are more readily absorbed than encapsulated or powder forms. A chondroprotective / restorative agent should enhance chondrocyte synthesis, increase synthesis of hyaluronic acid, inhibit enzymes that degrade cartilage, and reduce pain and synovitis. It must also slow down or reverse progression of the disease. The present invention, with it's unique combination of GS, CS, and HA is the closest yet to satisfying these criteria.

These three substances are the three connective tissue molecules needed to rebuild and synthesize new tissue.

Connective tissue is comprised mainly of collagen and proteglycans. Proteoglycans provide the framework for collagen and hold water, enhancing the flexibility and resistance to compression needed to counteract physical stress. The building blocks for all proteglycans are

amino sugars. Glucosamine is the building block needed as the precursor for all subsequent amino sugar synthesis. The formation of N-acetylglucosamine, chondroitin sulfate, and hyaluronic acid require glucosamine for their synthesis. In fact, glucosamine makes up 50% of the hyaluronic acid molecule.

Glucosamine sulfate along with Chondroitin sulfate have become very popular supplements administered in the treatment of degenerative joint disease. Recent studies have questioned whether the combination produces better results than Glucosamine sulfate alone. Also there is much debate over which glucosamine salt is preferred. Embodiments of the present invention utilize Glucosamine sulfate as it's source of Glucosamine. Most of the past and present research has been performed on the sulfated form. There is evidence that suggests that a component of the activity of GS and CS is related to the sulfate residues found in these compounds. Sulfur is an essential nutrient for the stabilization of the connective tissue matrix. It has been proposed that the sulfate molecules of GS and CS contribute to the therapeutic benefits of these compounds in degenerative joint disease. If this is true, it would suggest that GS, as opposed to N-acetylglucosamine and glucosamine HCl, is the best form of glucosamine supplementation. Recently, it has been shown that high-dose glucosamine may provide rapid symptomatic benefit and in the longer term aid the repair of damaged cartilage. The high does of glucosamine non only promotes synthesis of cartilage proteoglycans, but stimulates synovial production of hyaluronic acid. This would explain the anecdotal reports that a high does of glucosamine is beneficial.

SUMMARY AND DETAILED DESCRIPTION OF INVENTION

As previously explained, the present invention comprises a highly palatable formulation, which is the first to combine high levels of Glucosamine sulfate (GS) with Chondroitin sulfate (CS) and Hyaluronic Acid (HA) in an easy to absorb, low molecular weight formula.

Glucosamine, which is formed in the body as glucosamine 6-phosphate is the most fundamental building block required for the biosynthesis of the classes of compounds such as glucolipids, glycoproteins, glycosamineoglycans, hyaluronate, and proteoglycans. Directly or indirectly, glucosamine plays a role in the formation of articular surfaces, tendons, ligaments, synovial fluid, skin, bone, heart valves, blood vessels and mucus secretions of the digestive, respiratory, and urinary tracts. Glucosamine sulfate is greater than 90% absorbed and is quickly incorporated into articular cartilage following oral administration.

In one study, no LD50 was established for Glucosamine sulfate since even at very high levels (5000 mg/kg orally) there was no mortality in mice and rats. While treatment with GS does not produce the initial dramatic reductions in pain normally associated with NSAIDs, it's ability to reduce pain is consistent and progressive throughout the course of it's administration, resulting in a long-term improvement in the condition. Glucosamine is a small molecule and is very soluble in water.

Chondroitin Sulfate achieves benefits much more slowly than glucosamine. Chondroitin bioavailability following oral administration is around 15%. Because of its lower availability, the time needed to see a clinical response is lengthened. Chondroitin improves joint fluidity by drawing water to the cartilage tissue. When this water is drawn into the cartilage, it is

accompanied by nutrients which are supplied to the cartilage. Additionally, Chondroitin helps fight enzymes that inhibit transportation of nutrients into these tissues as it prevents other enzymes from tearing down cartilage tissue. Furthermore, Chondroitin, like Glucosamine, promotes the product of key cartilage components such as proteoglycans and it also prevents abnormal cell death.

Hyaluronic acid is a naturally occurring glycosaminoglycan. HA is a ubiquitous in the organism, with the highest concentration found in soft connective tissue and joint fluid. It is a constituent of the intercellular matrix of connective tissue that exists in almost all vertebrates. It plays an important role in a number of physiological functions, including protection and lubrication of cells, maintenance of the structural integrity of tissues, transport of molecules and cells, cell migration, cell function and differentiation, and fluid retention and regulation. The clinical benefits of HA in the horse are well published.

Hyaluronic acid is one of many glycosaminoglycans of physiological significance. Other are Chondroitin sulfate, Heparin sulfate, and Dermatan sulfate. The HA molecule is very similar to that of Chondroitin sulfate. In numerous studies, the oral absorption of CS, HS, and DS have been well documented. The bioavailabilities range from 15-20%. Hyaluronic acid has been shown to be absorbed through skin and reach the dermal lymphatics. Also, high levels of hyaluronan has been detected in the intestinal lymphatics. In addition, studies have been performed to determine the effects of HA secreted in saliva. Others have looked at hyaluronic acid production by oral epithelial cells. There is a beneficial effect when Glucosamine sulfate, Chondroitin sulfate, and Hyaluronic acid are administered orally. Generally, the oral

administration of embodiments of the present composition has a quicker clinical response than is produced when each component of the composition is given individually. A significant difference is an acute or a rapid relief in joint pain inflammation and swelling achieved by oral administration of the composition. A dramatic improvement over seven to ten days is achieved whereas it usually takes weeks for that effect to occur. Another benefit received is that of oral preparation and administration of HA given, for example, in the equine in any formulation. The administration of the HA composition orally and having a clinical effect eliminates more evasive procedures. Other ways to give HA would be more invasive, such as injection by IV or other administration into the joints. Basically, embodiments of the present invention may include an oral preparation that is less evasive and also may include an embodiment which is the only oral way to give HA. This provides another alternative to giving it by an injection.

Another benefit is that embodiments of the present invention, with it's high dose of Glucosamine sulfate, Hyaluronic acid, and Chondroitin sulfate, appears to have a synergistic effect which hastens the clinical response.

One embodiment of the present invention is a unique formulation that combines Glucosamine sulfate, Chondroitin sulfate, and Hyaluronic acid into a paste formulation for direct oral administration or top dressing feed. This is the only product available which combines these three substances which are critical for cartilage metabolism and production of synovial fluid. Also, this embodiment is the only oral paste formulation available for any one of these supplements. Early clinical trials have shown that when the three products are combined, they

have a synergistic effect. The clinical effects have been impressive. Data has shown a quicker clinical response when GS, CS, and HA are combined than when they are used individually.

Conditions in which embodiments of the present invention would be beneficial:

1) Osteoarthritis
2) Joint effusion
3) Joint inflammation and pain
4) Post operative arthroscopic surgery
5) Restoring proper joint function
6) Promote metabolic activity of chondrocytes (cartilage producing cells)
7) Inhibit enzymes that degrade cartilage
8) Stimulate the production of Hyaluronic acid

Embodiments of the present invention possess the following adavantages:

1) Only paste formulation on market
2) Only combination of GS, CS, HA in a paste formulation
3) Only oral paste form of Glucosamine
4) Only oral paste form of Chondroitin
5) Only oral paste form of Hyaluronic acid
6) Only oral paste in a molasses flavored base

One embodiment of the present invention possesses a molasses flavor. Other flavors would include apple, cherry, and any other palatable flavor.

One embodiment of the present invention comprises the following:

	Wt%
Glucosamine sulfate	46.03
Chondroitin sulfate	4.60
Sodium Hyaluronate	0.18
Manganese sulfate	0.18
Powdered sugar	8.70
Xanthan gum	0.10
Molasses	25.00
Water	14.00
Glycerine	0.70
Corn Starch	0.30
Sodium Benzoate	0.50

Embodiments of the present invention in a paste formulation has many advantages. When adding to feed, the formulation will stick to grain to insure total consumption. Embodiments of the paste formulation can be given orally (direct administration) or added to feed--depending on management of animals (turned out in field vs stall confinement). Other advantages include the following:

1) Better absorption with liquids

2) Molasses flavored paste--more palatable

3) Sticky consistency--animal cannot spit product from mouth which insures total dose

4) Syringe dose insures more accurate dose

5) Brown sugar included--more paltable

Effects of GS vs CS:

Glucosamine sulfate:

1)Enhances chondrocyte synthesis

2)Enhances synthesis of hyaluronic acid

3)Reduces joint pain

4)Reduces synovitis

Chondroitin sulfate:

1)Also helps with chondrocyte synthesis

2)CS has been found to inhibit degradative enzymes in cartilage

3)CS strengthens and enhances vessels that feed joints or supply them with nutrients by reducing arterial plaque and clear cholesterol deposits

4)Reduces joint pain and improves joint mobility

5)Reduces synovitis associated with joint arthritis

Neither GS or CS fulfills the quest for the ideal chondroprotective/restorative agent separately but when combined they appear to provide the necessary components for the health and wellbeing of the joint. Hyaluronic acid complements the combination by helping to restore the HA levels needed for joint health and lubrication which are decreased when synovitis is present.

Hyaluronic acid was discovered in 1934 by Meyer and Palmer. It is an important component of the intercellular matrix. HA is ubiquitous in the organism, with the highest level

in soft connective tissue. Specifically, the highest levels are found in the eye and synovial fluid of joints. In joints, its primary role is that of lubrication, reducing pain, and inflammation. In arthritic joints HA is deficient.

Hyaluronic acid is a glycosaminoglcan. Other glycosaminoglycans are Chondroitin sulfate, Heparin sulfate, and Dermatan sulfate. The most abundant GAG is Chondroitin sulfate. The three related GAGs have been found to be absorbed orally. Because of their chemical similarities and the clinical reports of improvement of synovitis, HA has a synergistic effect with GS and CS when given orally. This effect is observed as a more rapid clinical response than when GS and CS are given individually.

Clinically, responses are seen in 7 to 10 days vs three to four weeks or not at all when GS and CS are given without HA. Therefore, we have seen a dramatic decrease in synovitis when HA is combined with GS and CS. This leads us to conclude that HA is absorbed orally and effective either alone or in combination with GS and CS. Therefore, an additional embodiment of the invention comprises a composition including HA and any acceptable carrier, such as the paste formulation disclosed herein and any other liquid, powder, gel or similar type carrier.

Another embodiment of the invention includes a paste formulation containing the active component isoxuprine. Isoxuprine is a vasodilator and is utilized in treatment of many afflictions including the treatment of navicular disease. One effect of isoxuprine is that it stimulates the vasodilator nerves, such as the vaso-inhibitory and vasohypotonic nerves, and causes dilation or relaxation of the blood vessels. Administration of isoxuprine to a patient, such as an animal, in the form of a paste is beneficial to ensure adequate administration.

While the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications, and variations will be apparent to those skilled in the art in light of the foregoing description. Accordingly, it is intended to embrace all such alternatives, modifications, and variations which fall within the spirit and broad scope of the invention.

LOT I01013 # CHONDROGEN EQ PROCEDURE

BATCH SIZE:666.559 KG BULK DENSITY: 11.75LBS/GAL

REVISION NO: 1
SUPERCEEDS: 6/9/00
REASON FOR REV: BULK DENSITY CORECTION

	RAW MATERIAL	WT%	CODE #	CHARGE WTS(KG)	LBS	SOURCE	LOT NUMBER
1	GLUCOSAMINE SULFATE	36	8122	240	529.104	CHINA	20000503/200213
2	CHONDROITIN SULFATE	4	7844	26.644	58.73936	CHINA	H5000530
3	SODIUM HYALUROATE	0.144	3956	0.9599	2.116196	K3CORP	506
4	MANGANESE SULFATE	0.144	6909	0.9599	2.116196	JAPAN	10
5	POWDERED SUGAR 10X	20	1255	133.332	293.9437	FL CRYSTAL	861602A8-FC0741
6	GLYCERINE	0.7	9347	4.66662	10.28803	ETHOX	Q8R204
7	XANTHAN GUM	0.2	9399	1.33332	2.939437	KELZAN	ZN9D0917D
8	SODIUM BENZOATE	0.7	9517	4.66662	10.28803	BF GOODRICH	
9	CITRIC ACID ANHYDROUS	0.2	9114	1.33332	2.939437	CHINA	BBCD330560906
10	MOLASSES	23.5	1147	156.6651	345.3839	CHEMSOLVE	R000711
11	WATER DI	14.4		95.999	211.6394	CHEMSOLVE	
	TOTAL	**100**		**666.55978**	**1469.498**		

CHONDROGEN EQ

LOT NO I01013 PART 1 OF 5

BALL MILLING OPERATION FOR POWDERED PREMIX

DATE	TIME	OPER	
8/30	10:30	MB	RECEIVE 2@25KGS DRUMS OF GLUCOSAMINE SULFATE.
			CHECK CODE NUMBER AND WRITE IT DOWN HERE 8122
			CODE NUMBER MATCHES WITH **8122**
			HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO 2000853 SUPVSR INT P
			CHECK GROSS WEIGHT OF EACH DRUM 27 & 27
			HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT P INITIALS OF CHECK
	10:35	MB	CHARGE 50 KGS (110 LBS) OF GLUCOSAMINE SULFATE INTO THE BALL MILL
			CLOSE UP ANY PARTIAL DRUMS AND LIST PIECE WEIGHT 0
	10:40	MB	RECEIVE DRUM OF CHONDROITIN SULFATE 90%
			CHECK CODE NUMBER AND WRITE IT DOWN HERE 7844
			CODE NUMBER MATCHES WITH **7844**
			HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO H5200530 SUPVSR INT P
			WEIGH OUT 5.53 KGS (12.2 LBS) INTO A CLEAN NEW PAIL
			HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT _____ INITIALS OF CHECK
	10:40	MB	CHARGE CHONDROITIN INTO THE BALL MILL
			CLOSE UP ANY PARTIAL DRUMS AND LIST PIECE WEIGHT 12.2
	10:45	MB	RECEIVE SUGAR POWDERED CANE 10-X
			CHECK CODE NUMBER AND WRITE IT DOWN HERE 1255
			CODE NUMBER MATCHES WITH **1255**
			HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO 861602AR-FC074 SUPVSR INT P
			WEIGH OUT 27.7 KGS (61.1 LBS) OF SUGAR INTO A CLEAN PAIL
			HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT P INITIALS OF CHECK
	1050	MB	CHARGE SUGAR INTO THE BALL MILL
8/30	10:50	MB	TURN ON BALL MILL AND ALLOW TO MIX FOR 24 HOURS
8/31	10:41	MB	CHECK BATCH FOR PARTICLE SIZE
			PACKAGE INTO NEW 55 GAL OPEN HEAD POLY WITH POLY LINER
		MB	LABEL PWD PREMIX EQ

CHONDROGEN EQ

LOT NO E0103 PART 2 OF 5

BALL MILLING OPERATION FOR POWDERED PREMIX

DATE	TIME	OPER	
8/31	10⁰⁰	MB	RECEIVE 2@25KGS DRUMS OF GLUCOSAMINE SULFATE.
			CHECK CODE NUMBER AND WRITE IT DOWN HERE 8122
			CODE NUMBER MATCHES WITH **8122**
			HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO [illegible] SUPVRS INT P
			CHECK GROSS WEIGHT OF EACH DRUM 27 & 27
			HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT P INITIALS OF CHECK
	10²⁰	MB	CHARGE 50 KGS (110 LBS) OF GLUCOSAMINE SULFATE INTO THE BALL MILL
			CLOSE UP ANY PARTIAL DRUMS AND LIST PIECE WEIGHT 0
	10²⁰	MB	RECEIVE DRUM OF CHONDROITIN SULFATE 90%
			CHECK CODE NUMBER AND WRITE IT DOWN HERE 7844
			CODE NUMBER MATCHES WITH **7844**
			HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO H5200530 SUPVRS INT P
			WEIGH OUT 5.53 KGS (12.2 LBS) INTO A CLEAN NEW PAIL
			HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT P INITIALS OF CHECK
	10³⁰	MB	CHARGE CHONDROITIN INTO THE BALL MILL
			CLOSE UP ANY PARTIAL DRUMS AND LIST PIECE WEIGHT 20.6
	10³⁰	MB	RECEIVE SUGAR POWDERED CANE 10-X
			CHECK CODE NUMBER AND WRITE IT DOWN HERE 1255
			CODE NUMBER MATCHES WITH **1255**
			HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO 86160208-RC0211 SUPVRS INT P
			WEIGH OUT 27.7 KGS (61.1 LBS) OF SUGAR INTO A CLEAN PAIL
			HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT P INITIALS OF CHECK
	10⁴⁵	MB	CHARGE SUGAR INTO THE BALL MILL
			TURN ON BALL MILL AND ALLOW TO MIX FOR 24 HOURS
9/1	10⁰⁰	MB	CHECK BATCH FOR PARTICLE SIZE
			PACKAGE INTO NEW 55 GAL OPEN HEAD POLY WITH POLY LINER
		MB	LABEL POWDERED PREMIX EQ

CHONDROGEN EQ

LOT NO I01013 PART 3 OF 5

BALL MILLING OPERATION FOR POWDERED PREMIX

DATE	TIME	OPER	
9/1	10⁰⁰	MB	RECEIVE 2@25KGS DRUMS OF GLUCOSAMINE SULFATE.
			CHECK CODE NUMBER AND WRITE IT DOWN HERE 8122
			CODE NUMBER MATCHES WITH 8122
			HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO 20021303 SUPVRS INT P
			CHECK GROSS WEIGHT OF EACH DRUM 27 & 27
			HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT P INITIALS OF CHECK
	10³⁰	MB	CHARGE 50 KGS (110 LBS) OF GLUCOSAMINE SULFATE INTO THE BALL MILL
			CLOSE UP ANY PARTIAL DRUMS AND LIST PIECE WEIGHT 0
	10³⁰	MB	RECEIVE DRUM OF CHONDROITIN SULFATE 90%
			CHECK CODE NUMBER AND WRITE IT DOWN HERE 7844
			CODE NUMBER MATCHES WITH 7844
			HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO H5000530 SUPVRS INT P
			WEIGH OUT 5.53 KGS (12.2 LBS) INTO A CLEAN NEW PAIL
			HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT P INITIALS OF CHECK
	10⁴⁵	MB	CHARGE CHONDROITIN INTO THE BALL MILL
			CLOSE UP ANY PARTIAL DRUMS AND LIST PIECE WEIGHT 184
	10⁴⁵	MB	RECEIVE SUGAR POWDERED CANE 10-X
			CHECK CODE NUMBER AND WRITE IT DOWN HERE 1255
			CODE NUMBER MATCHES WITH 1255
			HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO 8616028-FC0711 SUPRV INT P
			WEIGH OUT 27.7 KGS (61.1 LBS) OF SUGAR INTO A CLEAN PAIL
			HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT P INITIALS OF CHECK
	10³⁰	MB	CHARGE SUGAR INTO THE BALL MILL
9/1	10⁵⁵	MB	TURN ON BALL MILL AND ALLOW TO MIX FOR 24 HOURS
9/2	9⁰⁰	MB	CHECK BATCH FOR PARTICLE SIZE
			PACKAGE INTO NEW 55 GAL OPEN HEAD POLY WITH POLY LINER
		MB	LABEL POWDERED PREMIX EQ

CHONDROGEN EQ

LOT NO E01013 PART 4 OF 5

BALL MILLING OPERATION FOR POWDERED PREMIX

DATE	TIME	OPER	
9/4	8:30	MB	RECEIVE 2@25KGS DRUMS OF GLUCOSAMINE SULFATE.
			CHECK CODE NUMBER AND WRITE IT DOWN HERE 8122
			CODE NUMBER MATCHES WITH **8122**
			HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO 20005013 SUPVRS INT P
			CHECK GROSS WEIGHT OF EACH DRUM 27 & 27
			HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT P INITIALS OF CHECK
	9:00	MB	CHARGE 50 KGS (110 LBS) OF GLUCOSAMINE SULFATE INTO THE BALL MILL
			CLOSE UP ANY PARTIAL DRUMS AND LIST PIECE WEIGHT _____
	9:00	MB	RECEIVE DRUM OF CHONDROITIN SULFATE 90%
			CHECK CODE NUMBER AND WRITE IT DOWN HERE 7844
			CODE NUMBER MATCHES WITH **7844**
			HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO 1+5[illegible]30 SUPVRS INT P
			WEIGH OUT 5.53 KGS (12.2 LBS) INTO A CLEAN NEW PAIL
			HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT P INITIALS OF CHECK
	9:20	MB	CHARGE CHONDROITIN INTO THE BALL MILL
			CLOSE UP ANY PARTIAL DRUMS AND LIST PIECE WEIGHT 6
	9:20	MB	RECEIVE SUGAR POWDERED CANE 10-X
			CHECK CODE NUMBER AND WRITE IT DOWN HERE 1255
			CODE NUMBER MATCHES WITH **1255**
			HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO 86[illegible]741 SUPVRS INT P
			WEIGH OUT 27.7 KGS (61.1 LBS) OF SUGAR INTO A CLEAN PAIL
			HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT P INITIALS OF CHECK
	9:40	MB	CHARGE SUGAR INTO THE BALL MILL
9/4	10:00	MB	TURN ON BALL MILL AND ALLOW TO MIX FOR 24 HOURS
9/5	8:30	MB	CHECK BATCH FOR PARTICLE SIZE
			PACKAGE INTO NEW 55 GAL OPEN HEAD POLY WITH POLY LINER
		MB	LABEL POWDERED PREMIX EQ

CHONDROGEN EQ

LOT NO I01013 PART 5 OF 5

BALL MILLING OPERATION FOR POWDERED PREMIX

DATE	TIME	OPER	
9/5	10⁰⁰	MB	RECEIVE 2@25KGS DRUMS OF GLUCOSAMINE SULFATE.
			CHECK CODE NUMBER AND WRITE IT DOWN HERE 8122
			CODE NUMBER MATCHES WITH **8122**
			HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO 2000503 SUPVRS INT P
			CHECK GROSS WEIGHT OF EACH DRUM 22 & 22
			HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT P INITIALS OF CHECK
	10³⁰	MB	CHARGE 40.4 KGS (89 LBS) OF GLUCOSAMINE SULFATE INTO THE BALL MILL
			CLOSE UP ANY PARTIAL DRUMS AND LIST PIECE WEIGHT 21.0
	10⁴⁰	MB	RECEIVE DRUM OF CHONDROITIN SULFATE 90%
			CHECK CODE NUMBER AND WRITE IT DOWN HERE 7844
			CODE NUMBER MATCHES WITH **7844**
			HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO H5D00530 SUPVRS INT P
			WEIGH OUT 4.48 KGS (9.88 LBS) INTO A CLEAN NEW PAIL
			HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT P INITIALS OF CHECK
	11⁰⁰	MB	CHARGE CHONDROITIN INTO THE BALL MILL
			CLOSE UP ANY PARTIAL DRUMS AND LIST PIECE WEIGHT 48.8
	11⁰⁰	MB	RECEIVE SUGAR POWDERED CANE 10-X
			CHECK CODE NUMBER AND WRITE IT DOWN HERE 1255
			CODE NUMBER MATCHES WITH **1255**
			HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO 86602AS-FC0741/SUPVRS INT P
			WEIGH OUT 22.5 KGS (49.5 LBS) OF SUGAR INTO A CLEAN PAIL
			HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT P INITIALS OF CHECK
	11²⁰	MB	CHARGE SUGAR INTO THE BALL MILL
9/5	11³⁰	MB	TURN ON BALL MILL AND ALLOW TO MIX FOR 24 HOURS
9/6	13⁰⁰	MB	CHECK BATCH FOR PARTICLE SIZE
			PACKAGE INTO NEW 55 GAL OPEN HEAD POLY WITH POLY LINER
		MB	LABEL POWDERED PREMIX EQ

		CHECK CODE NUMBER AND WRITE IT DOWN HERE 9114
		CODE NUMBER MATCHES WITH 9114
		HAVE THE SUPERVISOR VERIFY PRODUCT AND LOT NUMBER 3BC033052C9Pue SUPVRS INT
		WEIGH OUT 1.33 KGS (2.94 LBS) OF CITRIC ACID ANHYROUS
		HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT
1440	MB	ADD 1.33 KGS OF CITRIC ACID ANHYDROUS TO THE BATCH REACTOR
		MIX FOR 15 MINUTES
1800	MB	ADD THE XANTHAN/GLCERINE/WATER MIXTURE TO REACTOR
1900	MB	MIX FOR 1 HOUR
		EMPTY REACTOR AND WEIGH 2316

CHONDROGEN EQ

LOT NO F01013

XANTHAN GUM PREPARATION

DATE	TIME	OPER	
9/5	13[00]	MB	RECEIVE GYLCERINE
			CHECK THE CODE NUMBER AND WRITE IT DOWN HERE 9347
			CODE NUMBER MATCHES WITH 9347
			HAVE SUPERVISOR VERIFY PRODUCT AND LOT NUMBER GGR204 SUPVRS INT T
			WEIGH OUT 4.66 KGS (10.28 LBS) OF GYLCERINE
	13[0]	MB	CHARGE MATERIAL INTO BLENDER
	13[10]	MB	RECEIVE THE XANTHAN GUM
			CHECK THE CODE NUMBER AND WRITE IT DOWN HERE 9399
			CODE NUMBER MATCHES WITH 9399
			HAVE THE SUPERVISOR VERIFY PRODUCT AND LOT NUMBER 3NQDC917D SUPVRS INT T
			WEIGH OUT 1.33 KGS (2.93 LBS) OF XANTHAN GUM
	15[00]	MB	CHARGE MATERIAL SLOWLY INTO BLENDER AND MIX
	16[00]	MB	WHEN CONSISTANT MIXTURE -DILUTE BY ADDING 11.6 LBS OF DI WATER TO MIXTURE
			MIX FOR 2- 3 HOURS OR LONGER

CHONDROGEN EQ

LOT NO EQ1013 PART 1 OF 2

LIQUID/ SALTS MIXTURE PRPARATION

DATE	TIME	OPER	
			IN THE REACTOR, PREPARE FOR THE ADDITION OF SODIUM HYALURONATE
9/5	1320	MB	WEIGH OUT 90.7 KGS (200 LBS) OF DISTILLED WATER
	1340	MB	CHARGE INTO THE REACTOR
		MB	TURN ON AGITATOR
9/5	1340	MB	RECEIVE SODIUM HYALURONATE
			CHECK CODE NUMBER AND WRITE IT DOWN HERE 3956
			CODE NUMBER MATCHES WITH 3956
			HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO 000506 SUPVRS INT P
			WEIGH OUT 951GRAMS OF SODIUM HYALURONATE
			HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT P INITIALS OF CHECK
			CHARGE SLOWLY BY SPRINKLING IN OVER 1 HR SPAN
			AGITATE
	1340	MB	RECEIVE MAGANESE SULFATE
			CHECK CODE NUMBER AND WRITE IT DOWN HERE 6909
			CODE NUMBER MATCHES WITH 6909
			HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO 10 SUPVRS INT P
			WEIGH OUT 952 GRAMS OF MANGANESE SULFATE
			HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT P INITIALS OF CHECK
	1400	MB	ADD 952 GRAMS OF MANGANESE SULFATE TO THE BATCH REACTOR
			AGITATE
			MIX FOR 15 MINUTES
	1420	MB	RECEIVE THE SODIUM BENZOATE
			CHECK CODE NUMBER AND WRITE IT DOWN HERE 9517
			CODE NUMBER MATCHES WITH 9517
			HAVE SUPERVISOR VERIFY PRODUCT AND LOT NUMBER NONE SUPVRS INT P
			WEIGH OUT 4.67 KGS (10.29 LBS) OF SODIUM BENZOATE
			HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT P INITIALS OF CHECK
	1440	MB	ADD 4.67 KGS OF SODIUM BENZOATE TO THE BATCH REACTOR
			MIX FOR 15 MINUTES
	1500	MB	RECEIVE THE CITRIC ACID ANHYDROUS

CHONDROGEN EQ

LOT NO E01013 PART 2 OF 2

LIQUID PREMIX FOR EQ

DATE	TIME	OPER	
			IN BATCH REACTOR PREPARE FOR FINAL BLENDING OF LIQUID COMPONENTS
9/7	8:30	JAB	RECEIVE MOLASSES
			CHECK CODE NUMBER AND WRITE IT DOWN HERE 1147
			CODE NUMBER MATCHES WITH 1147
			HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO. R000711 SUPRVSR INT J
	9:00	JAB	CHARGE 156.67KGS (345.4 LBS) OF MOLASSES INTO REACTOR
		JAB	TURN ON AGITATOR
	9:45	JAB	CHARGE LIQUID SALTS PREMIX TO REACTOR
	13:00	JAB	MIX FOR 4 HOURS
			DISCHARGE INTO NEW POLY DRUMS
			WEIGH 5 76
		JAB	LABEL LIQUID PREMIX EQ

CHONDROGEN EQ

LOT NO I01013

DISPERSING POWDER AND LIQUID PREMIX TOGETHER

DATE	TIME	OPER	
9/5	700	VM	IN A BATCH DISPERSER, SET UP FOR CHONDROGEN EQ
		VM	ADJUST FOR SOLID FEED
		VM	ADJUST FOR LIQUID FEED
		VM	BLEND MATERIALS AND PACKAGE
	800	VM	START
	1100	VM	FINISH
		VM	WEIGHT OF FINAL PRODUCT 1340

CHONDROGEN EQ

LOT NO I 01013

PACKAGING FROM DRUMS TO PAILS

DATE	TIME	OPER	
9/18	3:00	[illegible]	RECEIVE APPROVED MATERIAL CHONDROGEN EQ
		[illegible]	VERIFY LOT NO
		[illegible]	PACKAGE INTO 5 GAL CLEAN OPEN HEAD POLY PAILS AT 50 LBS NET
		[illegible]	LABEL

WRITE DOWN NUMBER OF PAILS AND PIECE

PAILS @ 50LBS NET 26

PIECE @ 32 LBS NET

TOTAL WEIGHT 1332

CHONDROGEN EQ

LOT NO E01013

DATE	TIME	TECH	
9/18	4:00p	[illegible]	SAMPLE RECEIVED
9/18	4:00p	[illegible]	TEST FOR PH (5%) 4.1
9/18	4:00p	[illegible]	TEST FOR VISCOSITY 18,000

ACTUAL LOT ANALYSIS: SODIUM HYALURONATE, Powder

SPECIFICATION NO. 4917-13-EL

Description: Fine white powder, with no odor

Actual Lot Analysis:	*Specification*	*Actual*
a) Estee Lauder Requirements:		
Infrared Spectrum	To Pass Test	Passes
pH of a 0.5% aqueous solution	6 - 8	7.3
Water Content (KF)	≤ 10%	5.8%
Residue On Ignition	7 - 10%	7.6%
Protein Content	≤0.1%	<0.1%
Uronic Acid Content (dry basis)	45.0-48.4%	47.8%
Sodium Hyaluronate (dry basis)	93-100%	98.8%
Total Aerobic Plate Count	≤1000 CFU/g	Passes
Non-Conforming Organisms	None Recovered	Passes
b) Other Parameters		
Solubility @ 0.5% W/V in freshly distilled H_2O	*Complete*	*Passes*
Appearance of a 0.5% aqueous solution (clear-slightly opalescent-colorless viscous liquid)	*To Pass Test*	*Passes*
Total Nitrogen (dry basis)	*3.0 - 3.6%*	*3.4%*
Sodium Glucuronate (dry basis)	*51.2 - 53.9%*	*53.2%*
Molecular Weight	*1.5 - 1.9x10⁶*	*1.65x10⁶*
Preservative	*None*	*None*

Shelf Life: 2 years

Packing: 500 g poly containers with tamper-proof safety seals

Lot Size: 10 kg

Approval:

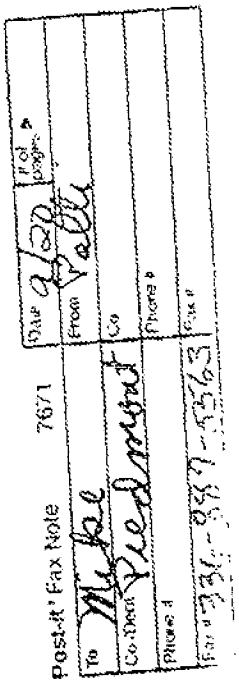
K.I

CERTIFICATE OF ANALYSIS

Commodity: **D-Glucosamine Sulfate.2KCL**
Date of Analysis: 5/23/00 Batch No.: 20000503

	Guaranteed Specification	Test Result
Appearance:	White Crystalline Powder	Conforms
Assay:	98% - 101%	99.2%
$-[\alpha]^{20}_{D}$:	+49° - +55°	+49.9°
Loss on drying:	≤0.5%	0.38%
Residue on ignition:	26.5% - 29.8%	28.2%
Iron (Fe):	<10ppm	<10ppm
Heavy Metals:	≤10ppm	<10ppm
Arsenic:	≤0.5ppm	<0.5ppm
pH Value:	3.0 – 5.0	4.5
Chloride:	11.2% - 12.3%	12.0%
Bulk Density:	≥0.85g/cc	0.89g/cc
Total Plate Count:	<5000cfu/g	487cfu/g
Yeast & Mold:	<100cfu/g	37cfu/g
E. Coli:	Negative	Negative
Salmonella:	Negative	Negative

Packing: 25kg net each fiber drum with double PE liner.
Quantity: 1,000kg = 40 x 25kg drums



Certificate of Analysis

Product Name: Chondroitin Sulfate 90% Min.

Batch No.: HS000530

Assay:	90% Min.	91.7%
Loss on Drying:	10% Max.	8.6%
PH:	5.5 – 7.5	6.4
Bulk Density:	0.6 g/ml Min.	0.68 g/ml
Nitrogen:	2.5% - 3.8%	3.1%
Heavy Metal:	10 ppm Max.	9.4 pm
Chloride:	1% Max.	Pass
Other Bacterium:	300/g Max.	Pass
Mold:	100/g Max.	Pass
Clear Degree:	Transparent	Pass

NOTE THE ABOVE INFORMATION IS BASED ON THE CERTIFICATE OF ANALYSIS RECEIVED FROM OUR SUPPLIER AND IS NOT INTENDED AS A SUBSTITUTE FOR STRICT QUALITY CONTROL ANALYSIS BY THE PURCHASER OF THIS PRODUCT

MATERIAL SAFETY DATA SHEET

T: CHONOROGEN EQ

MSDS NO: 88-581A

SECTION 1: GENERAL INFORMATION

HMIS & NFPA RATING

A HMIS HAZARD RATING

I:	0	LEAST
	0	LEAST
IVITY:	0	LEAST
AL PROTECTION:	X	ASK SUPERVISOR

NFPA 704 DERIVED HAZARD RATING

HEALTH:	0	LEAST
FIRE:	0	LEAST
REACTIVITY:	0	LEAST
OTHER:	X	ASK SUPERVISOR

SECTION 2: HAZARDOUS INGREDIENTS

HAZARD CLASSIFICATION: NONHAZARDOUS

OUS INGREDIENTS	CAS#	HAZARD	LIMITS
DIENTS CURRENTLY NOT OUS IN ACCORDANCE TO 9 1910.1200.			

SECTION 3: PHYSICAL DATA

	N.A.	N	%
ILITY IN WATER:	SOLUBLE		
FIC GRAVITY:	N.D.		
RANCE:	OPAQUE BROWN PASTE		

ND = NOT DETERMINED NA = NOT APPLICABLE

T: CHONDROGEN EQ MSDS NO: 88-581A

SECTION 4: FIRE AND EXPLOSION DATA

POINT: N.A.

UISHING METHOD: USE WATER, CARBON DIOXIDE, DRY CHEMICAL OR FOAM.

L FIRE FIGHTING PROCEDURES: USE SELF CONTAINED BREATHING APPARATUS.

L FIRE FIGHTING PROCEDURES: NONE KNOWN.

SECTION 5: REACTIVITY DATA

ITY STABLE
OUS POLYMERIZATION: WILL NOT OCCUR
POSITION PRODUCTS: NOT ESTABLISHED.
IONS AND MATERIALS TO AVOID: NONE KNOWN.

SECTION 6: HEALTH HAZARD DATA

OF EXPOSURE: EYES YES SKIN YES INGESTION YES INHALATION YES

SYMPTOMS OR ACUTE HEALTH HAZARDS

MAY CAUSE EYE IRRITATION.

NO EFFECTS EXPECTED UNDER NORMAL USE.

TION: NOT ESTABLISHED.

ATION: NO EFFECTS EXPECTED UNDER NORMAL USE.

IC HEALTH HAZARDS: NOT ESTABLISHED

NOGENICITY: NTP IARC OSHA

FIRST AID

FLUSH EYES WITH WATER FOR AT LEAST 15 MINUTES.
IF IRRITATION OCCURS, GET MEDICAL ATTENTION.
WASH EXPOSED AREAS WITH SOAP AND WATER. IF IRRITATION
PERSIST, SEEK MEDICAL ATTENTION.
TION: INDUCE VOMITING BY GIVING 2 GLASSES OF WATER AND PLACE
FINGER DOWN THROAT. CALL A PHYSICIAN. NEVER GIVE
ANYTHING BY MOUTH TO AN UNCONSCIOUS PERSON.
ATION: IF AFFECTED, REMOVE INDIVIDUAL TO FRESH AIR.

ND = NOT DETERMINED NA = NOT APPLICABLE

.T: CHONDROGEN EQ MSDS NO: 88-581A

SECTION 7: PRECAUTIONS FOR SAFE HANDLING AND STORAGE

VENTILATE AREA, PERSONS PERFORMING CLEAN-UP SHOULD WEAR ADEQUATE PROTECTION EQUIPMENT. CONTAIN MATERIAL BY DIKING THE AREA AROUND THE SPILL. IF THE PRODUCT IS IN A SOLID FORM, SHOVEL DIRECTLY INTO RECOVERY DRUMS. IF THE PRODUCT IS A LIQUID, IT SHOULD BE PICKED UP USING A SUITABLE ABSORBANT MATERIAL, THEN SHOVELED TO RECOVERY DRUMS. IF THE MATERIAL IS RELEASED INTO THE ENVIRONMENT, THE USER SHOULD DETERMINE WHETHER THE SPILL SHOULD BE REPORTED TO THE APPROPRIATE LOCAL, STATE, AND FEDERAL AUTHORITIES.

DISPOSAL METHOD: CONSULT LOCAL, STATE, AND FEDERAL REGULATIONS BEFORE OF THIS MATERIAL.

:NG AND STORAGE: MATERIAL SHOULD BE STORED IN ITS OWN CONTAINER AND SHOULD ALWAYS BE KEPT COVERED WHEN NOT IN USE

SECTION 8: PROTECTIVE EQUIPMENT

:ATORY PROTECTION: NONE NORMALLY NEEDED.

LATION: NO SPECIAL REQUIREMENTS.

:TIVE EQUIPMENT: GLOVES ____ FACESHIELD ____ APRON ____ GOGGLES YES IMPERVIOUS COVERALLS ____

:YGIENIC PRACTICES: AS WITH ALL INDUSTRIAL CHEMICALS, CARE SHOULD BE TAKEN TO AVOID CONTACT WITH EYES, SKIN, AND CLOTHING. HANDS AND UNPROTECTED SKIN SHOULD BE THOROUGHLY WASHED AND CONTAMINATED CLOTHING SHOULD BE CHANGED PRIOR TO ANY DIRECT PERSONAL CONTACT. ALL EXPOSED CLOTHING SHOULD BE LAUNDERED PER NORMAL CARE INSTRUCTIONS BEFORE REUSE.

SECTION 9: REGULATORY DATA

IT: SARA: THE FOLLOWING DATA IS BEING SUPPLIED IN COMPLIANCE WITH TITLE III SUPERFUND AMENDMENTS AND REAUTHORIZATION ACT (SARA) PART 313 AND 40 CFR 372:

THIS PRODUCT DOES NOT CONTAIN ANY CHEMICALS FOUND ON THE SARA LIST IN 40 CFR 372.

PORTATION: NOT REGULATED BY D.O.T.

ORNIA PROPOSITION 65: CONTAINS NO MATERIALS KNOWN TO BE ON THE CALIFORNIA PROPOSITION 65 LIST

SECTION 10: TOXICOLOGY

NO DATA AVAILABLE FOR CHRONIC OVEREXPOSURE.

DISCLAIMER

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MATERIAL SAFETY DATA SHEET

: PWD PREMIX EQ — MSDS NO: 00-101A

SECTION 1: GENERAL INFORMATION

HMIS & NFPA RATING

HMIS HAZARD RATING		NFPA 704 DERIVED HAZARD RATING	
:	0 LEAST	HEALTH:	0 LEAST
	0 LEAST	FIRE:	0 LEAST
VITY:	0 LEAST	REACITVITY:	0 LEAST
AL PROTECTION:	X ASK SUPERVISOR	OTHER:	X ASK SUPERVISOR

SECTION 2: HAZARDOUS INGREDIENTS

HAZARD CLASSIFICATION: NONHAZARDOUS

OUS INGREDIENTS	CAS#	HAZARD	LIMITS
IENTS CURRENTLY NOT OUS IN ACCORDANCE TO 1910.1200.			

SECTION 3: PHYSICAL DATA

	N.A. N %
LITY IN WATER:	SOLUBLE
IC GRAVITY:	N.D.
ANCE:	OPAQUE BROWN PASTE

ND = NOT DETERMINED NA = NOT APPLICABLE

T: PWD PREMIX EQ MSDS NO: 88-101A

SECTION 4: FIRE AND EXPLOSION DATA

>OINT: N.A.

JISHING METHOD: USE WATER, CARBON DIOXIDE, DRY CHEMICAL OR FOAM.

L FIRE FIGHTING PROCEDURES: USE SELF CONTAINED BREATHING APPARATUS.

L FIRE FIGHTING PROCEDURES: NONE KNOWN.

SECTION 5: REACTIVITY DATA

ITY STABLE
OUS POLYMERIZATION: WILL NOT OCCUR
OSITION PRODUCTS: NOT ESTABLISHED.
IONS AND MATERIALS TO AVOID: NONE KNOWN.

SECTION 6: HEALTH HAZARD DATA

OF EXPOSURE: EYES YES SKIN YES INGESTION YES INHALATION YES

SYMPTONS OR ACUTE HEALTH HAZARDS

MAY CAUSE EYE IRRITATION.

NO EFFECTS EXPECTED UNDER NORMAL USE.

ION: NOT ESTABLISHED.

TION: NO EFFECTS EXPECTED UNDER NORMAL USE.

C HEALTH HAZARDS: NOT ESTABLISHED

OGENICITY: NTP ARC OSHA

FIRST AID

FLUSH EYES WITH WATER FOR AT LEAST 15 MINUTES.
IF IRRITATION OCCURS, GET MEDICAL ATTENTION.
WASH EXPOSED AREAS WITH SOAP AND WATER. IF IRRITATION
PERSIST, SEEK MEDICAL ATTENTION.

ION: INDUCE VOMITING BY GIVING 2 GLASSES OF WATER AND PLACE
FINGER DOWN THROAT. CALL A PHYSICIAN. NEVER GIVE
ANYTHING BY MOUTH TO AN UNCONSCIOUS PERSON.

TION: IF AFFECTED, REMOVE INDIVIDUAL TO FRESH AIR.

ND = NOT DETERMINED NA = NOT APPLICABLE

T: PWD PREMIX EQ MSDS NO: 00-101A

SECTION 7: PRECAUTIONS FOR SAFE HANDLING AND STORAGE

VENTILATE AREA, PERSONS PERFORMING CLEAN-UP SHOULD WEAR ADEQUATE PROTECTION EQUIPMENT. CONTAIN MATERIAL BY DIKING THE AREA AROUND THE SPILL. IF THE PRODUCT IS IN A SOLID FORM, SHOVEL DIRECTLY INTO RECOVERY DRUMS. IF THE PRODUCT IS A LIQUID, IT SHOULD BE PICKED UP USING A SUITABLE ABSORBANT MATERIAL, THEN SHOVELED TO RECOVERY DRUMS. IF THE MATERIAL IS RELEASED INTO THE ENVIRONMENT, THE USER SHOULD DETERMINE WHETHER THE SPILL SHOULD BE REPORTED TO THE APPROPRIATE LOCAL, STATE, AND FEDERAL AUTHORITIES.

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SECTION 8: PROTECTIVE EQUIPMENT

ATORY PROTECTION: NONE NORMALLY NEEDED.

ATION: NO SPECIAL REQUIREMENTS.

TIVE EQUIPMENT: GLOVES ___ FACESHIELD ___ APRON ___ GOGGLES YES IMPERVIOUS COVERALLS ___

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ORTATION: NOT REGULATED BY D.O.T.

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SECTION 10: TOXICOLOGY

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MATERIAL SAFETY DATA SHEET

T: LIQ PREMIX EQ | MSDS NO: 00-102A

SECTION 1: GENERAL INFORMATION

HMIS & NFPA RATING

A HMIS HAZARD RATING		NFPA 704 DERIVED HAZARD RATING	
:	0 LEAST	HEALTH:	0 LEAST
	0 LEAST	FIRE:	0 LEAST
VITY:	0 LEAST	REACITVITY:	0 LEAST
AL PROTECTION:	X ASK SUPERVISOR	OTHER:	X ASK SUPERVISOR

SECTION 2: HAZARDOUS INGREDIENTS

HAZARD CLASSIFICATION: NONHAZARDOUS

OUS INGREDIENTS	CAS#	HAZARD	LIMITS
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SECTION 3: PHYSICAL DATA

	N.A.
LITY IN WATER:	SOLUBLE
IC GRAVITY:	N.D.
ANCE:	OPAQUE BROWN PASTE

ND = NOT DETERMINED NA = NOT APPLICABLE

': LIQ PREMIX EQ — MSDS NO: 88-102A

SECTION 4: FIRE AND EXPLOSION DATA

'OINT: N.A.

)ISHING METHOD: USE WATER, CARBON DIOXIDE, DRY CHEMICAL OR FOAM.

. FIRE FIGHTING PROCEDURES: USE SELF CONTAINED BREATHING APPARATUS.

. FIRE FIGHTING PROCEDURES: NONE KNOWN.

SECTION 5: REACTIVITY DATA

ITY: STABLE
)US POLYMERIZATION: WILL NOT OCCUR
)SITION PRODUCTS: NOT ESTABLISHED.
IONS AND MATERIALS TO AVOID: NONE KNOWN.

SECTION 6: HEALTH HAZARD DATA

OF EXPOSURE: EYES YES SKIN YES INGESTION YES INHALATION YES

SYMPTONS OR ACUTE HEALTH HAZARDS

MAY CAUSE EYE IRRITATION.

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TION: NO EFFECTS EXPECTED UNDER NORMAL USE.

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: LIQ PREMIX EQ MSDS NO: 00-102A

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SECTION 8: PROTECTIVE EQUIPMENT

TORY PROTECTION: NONE NORMALLY NEEDED.

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IVE EQUIPMENT: GLOVES ___ FACESHIELD ___ APRON ___ GOGGLES YES IMPERVIOUS COVERALLS ___

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SECTION 10: TOXICOLOGY

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ND = NOT DETERMINED NA = NOT APPLICABLE

CLAIMS:

1. A Chondroprotective/Restorative composition as disclosed and suggested herein.

2. A method of using a Chondroprotective/Restorative composition as disclosed and described herein.

3. A Chondroprotective/Restorative composition comprising Glucosamine sulfate (GS), Chondroitin sulfate (CS) and Hyaluronic Acid (HA) and optionally a pharmaceutically acceptable carrier.

4. A Chondroprotective/Restorative composition comprising Hyaluronic Acid (HA) and optionally a pharmaceutically acceptable carrier.

5. A composition comprising Isoxuprine and optionally a pharmaceutically acceptable carrier in an orally administered form.

6. The composition of claim 3 and 4 wherein the composition is in an orally administered paste form.

7. The composition of claim 3 and 4 wherein the composition is in an orally administered liquid form.

8. The composition of claims 3 and 4 wherein the composition is in an orally administered solid form.

9. A method of treating or preventing osteoarthritis, joint effusion, joint inflammation and pain, post operative arthroscopic surgery, deterioration of proper joint function, the reduction or inhibition of metabolic activity of

chondrocytes (cartilage producing cells), the activity of enzymes that degrade cartilage, the reduction or inhibition of the production of Hyaluronic acid comprising administering to a species a therapeutically effective amount of a composition including Glucosamine sulfate (GS), Chondroitin sulfate (CS) and Hyaluronic Acid (HA).

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(54) CHONDROPROTECTIVE/RESTORATIVE COMPOSITIONS AND METHODS OF USE THEREOF

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(57) ABSTRACT

The instant invention provides a method of treating or preventing osteoarthritis, joint effusion, joint inflammation and pain, synovitis, lameness, post operative arthroscopic surgery, deterioration of proper joint function including joint mobility, the reduction or inhibition of metabolic activity of chondrocytes, the activity of enzymes that degrade cartilage, the reduction or inhibition of the production of Hyaluronic acid, said method comprising orally administering to a mammalian species a therapeutically effective amount of Hyaluronic Acid or pharmaceutically acceptable salts thereof. Additionally, compositions containing hyaluronic acid; chondroitin sulfate, and glucosamine sulfate in a paste formulation are also disclosed which can be administered on their own or can be used as a feed additive.

CHONDROPROTECTIVE/RESTORATIVE COMPOSITIONS AND METHODS OF USE THEREOF

FIELD OF INVENTION

[0001] The present invention relates to medically useful preparations based on hyaluronic acid and pharmaceutically acceptable salts thereof, a naturally-occurring substance found in animal tissue, and especially in rooster comb, vitreous humour, umbilical cords, and synovial fluid of mammals. This invention also relates to new orally administrable formulations containing hyaluronic acid. The instant invention is also directed to chondroprotective/restorative compositions containing hyaluronic acid. This invention also relates to new pharmaceutical formulations containing hyaluronic acid. The invention is further directed to a new veterinary formulations containing hyaluronic acid. This invention further relates to orally administrable veterinary formulation containing hyaluronic acid.

[0002] The present invention is also directed to veterinary formulations containing hyaluronic acid and additional bio-effective active ingredients such as bioactive agents useful in the treatment of domesticated animals especially horses. This invention also provides methods for treating horses in need of chondroprotection. The invention is further directed to pharmaceutical compositions containing hyaluronic acid, glucosamine and chondroitin. The present invention also relates to a method of treating aseptic synovitis in horses with hyaluronic acid alone or in combination with other active ingredients. More specifically, the present invention is also intended for therapeutic treatments of arthritis and related conditions using pharmaceutical compositions containing hyaluronic acid as well as other active ingredients effective ion the treatment of joint diseases. The compositions of the invention are particularly useful in the veterinary field but are also very useful in treatment of humans.

[0003] This invention further relates to the oral administration of forms of hyaluronic acid and pharmaceutically acceptable salts thereof such as sodium hyaluronate, and orally administrable dosage forms containing forms of hyaluronic acid, for the prevention and/or treatment of diseases such as osteoarthritis, joint effusion, joint inflammation and pain, synovitis, and many other diseases associated with cartilage degeneration.

[0004] The instant invention also provides gels of hyaluronic acid with carboxymethylcellulose.

BACKGROUND OF THE INVENTION

[0005] Hyaluronic acid (HA) exists as a naturally-occurring polysaccharide (also known as a mucoid polysaccharide) that can be extracted from such diverse sources as rooster comb, umbilical cord, vitreous humor, synovial fluid, pathologic joints, skin and group A and C hemolytic Streptococci. The hyaluronic acid is also defined as a high viscosity naturally occurring glycosaminoglycan having a polymeric structure containing alternating N-acetyl-D-glucosamine and D-glucuronic acid monosaccharide units linked with β 1-4 bonds and the disaccharide units linked with β 1-3 glycoside bonds. It occurs usually as the sodium salt and has a molecular weight range of about 50,000 to 8×10^6 Daltons.

[0006] Hyaluronic acid is a naturally occurring glycosaminoglycan. HA is ubiquitous in the organism, with the highest concentration found in soft connective tissue and joint fluid. It is a constituent of the intercellular matrix of connective tissue that exists in almost all vertebrates. It plays an important role in a number of physiological functions, including protection and lubrication of cells, maintenance of the structural integrity of tissues, transport of molecules and cells, cell migration, cell function and differentiation, and fluid retention and regulation. The clinical benefits of intra-articular HA in the horse are well published.

[0007] Natural Hyaluronic acid is polydisperse in respect of molecular weight and is known to show excellent biocompatibility even when implanted or injected into the body by virtue of the absence of species and organ specificity. However, because of the relatively short in vivo residence time of Hyaluronic acid solution in biological applications, improvements in the persistency of Hyaluronic acid by chemical crosslinking with various chemical modifiers has been attempted to broaden its use for medical materials.

[0008] The isolation and characterization of Hyaluronic acid is described in Meyer et al, J. Biol. Chem. 107, 629 (1934); J. Biol. Chem. 114, 689 (1936); Balazs, Fed. Proc. 17, 1086 (1958); Laurent et al; Biochim. Biophys. Acta 42, 476 (1960). The structure of Hyaluronic acid was elucidated by Weissman et al, J. Am. Chem. Soc. 76, 1753 (1954) and Meyer, Fed. Proc. 17, 1075 (1958).

[0009] Hyaluronic acid is an important component of the intercellular matrix. Specifically, the highest levels are found in the eye and synovial fluid of joints. In joints, its primary role is that of lubrication, reducing pain, and inflammation. In arthritic joints HA is deficient. In regards to the joints, synovial fluid supplies nutrition to the articular cartilage and has incomparable functions as a lubricant and a shock absorber. It is clarified that its excellent viscoelastisity heavily owes to one of the main components, Hyaluronic acid. Concentration and molecular weight analyses of Hyaluronic acid demonstrated the concentration and molecular weight of Hyaluronic acid in the synovial fluid from patients with arthritis such as osteoarthritis and chronic articular rheumatism generally tended to be lower than in normal synovial fluid, and the lower concentration and molecular weight of Hyaluronic acid were closely associated with development of locomotor dysfunction and pain attributable to the weaker lubricating action and the weaker protecting action on the surface of the articular cartilage of synovial fluid.

[0010] Degradation of the structures in articular cartilage is a typical characteristic of all diseases resulting in chronic destruction of the joint structures. Examples of such disorders are rheumatoid arthritis, psoriatic arthritis, and osteoarthrosis. Also, acute inflammation of a joint is often accompanied by destruction of the cartilage, although in most cases this will not develop into the chronically destructive disease. It is not known which factors are crucial for the acutely inflamed joint to either proceed to healing or develop into the chronic process. Examples of diseases involving acute joint inflammation are yersinia arthritis, pyrophosphate arthritis, gout arthritis (arthritis urica), septic arthritis and various forms of arthritis of traumatic etiology.

[0011] Among other factors potentially conducive to the destruction of articular cartilage may be mentioned, for

instance, treatment with cortisone; this has been known for a long time to accelerate the degenerative process in osteoarthrosis.

[0012] Such a so-called "steroid arthropathy" occurs far too often as an undesirable side effect of intra-articular cortisone treatment and can be avoided only by providing for a sufficiently long period of rest after the treatment. Steroid arthropathy is characterized by an advanced degree of articular destruction and X-ray-detectable changes of the same type as occur in advanced degenerative articular disease (Nizolek, D H & White, K K, Cornell Vet. 1981, 71:355-75). According to what is at present accepted as an explanation of the degenerative arthropathy development following treatment with cortisone, this arthropathy is believed to be caused by a primary effect on the chondrocyte metabolism. It should be noted, however, that the actual conditions prevailing in cases of arthritis with severe inflammation of the joint are of a rather more complex character, since in those cases injection of cortisone appears to have an overall positive effect on the clinical picture.

[0013] Also, it is well known that articular cartilage is composed of about 70% of water, chondrocytes and a cartilage matrix. The major components constituting the articular matrix are collagen and proteoglycan; the proteoglycan having good water retention characteristics is contained in the network of collagen having a reticulated structure. The articular matrix is rich in viscoelasticity and has an important role in reducing the stimulus and load imposed on the cartilage in order to maintain the normal morphology and function of the articular cartilage.

[0014] Osteoarthritis and rheumatoid arthritis are representative of the diseases accompanied by the destruction of the cartilage matrix. It is thought that the destruction of the matrix in these diseases is triggered by mechanical stresses with aging in the case of osteoarthritis and by excess proliferation of the surface layer cells of the synovial membrane, pannus formation and inflammatory cell infiltration in the case of rheumatoid arthritis, and both phenomena are caused through the induction of proteases. Since the degradation of articular cartilage is progressed in the extracellular region at a neutral pH, it is said that a matrix metalloprotease (hereinafter referred to as "MMP" or "MMPs" when used as the general term) whose optimal pH is in the neutral range plays a leading role in the degradation.

[0015] No medical cure exists for osteoarthritis. The progressive degeneration of the joint due to osteoarthritis is irreversible. Present therapies are directed to palliative medical therapies to reduce inflammation and pain and surgical therapies to reconstruct an affected joint or, in severe cases, to replace the joint with an artificial, prosthetic joint.

[0016] Injection of high molecular weight Hyaluronic acid solution into diseased joints has been widely adopted as an effective measure for osteoarthritis among those articular diseases, and the source of high purity HA preparations for this purpose is cockscombs. Such HA preparations from cockscombs are biologically inherent and quite safe but usually have to be administered as frequently as several to 10 times to show significant therapeutic effect. Persistency tests on rabbits revealed that HA with a molecular weight of less than 1000000 administered into the knee joint cavities disappeared from the knee joint cavities in 1 to 3 days and suggested the need of frequent administrations (Blood Coagulation and Fibrinolysis, vol 12, 173,1992).

[0017] On the other hand, the molecular weight of HA found in the living body is reported to be as high as millions to 10000000, and a crosslinked HA derivative obtained by treatment with a chemical crosslinker has been developed as a therapeutic agent for knee joints with the idea that high molecular weight HA closer to the biologically intact one is likely to have higher effect. Reportedly, the crosslinked HA persisted for a period as long as 20 to 30 days after administration into rabbit knee joint cavities in the above-mentioned persistency tests and produced sufficient effect when administered three times in clinical tests, and is practically used as a therapeutic agent for arthritis (Journal of Rheumatology vol.20, 16, 1993).

[0018] A need exists for an effective palliative medication for the treatment of osteoarthritis and other joint diseases which is both safe and effective when used for both short-term and long-term therapy and which can be administered orally.

OBJECTS OF THE INVENTION

[0019] It is a first object of the present invention to provide a method for treating mammals having joint diseases by oral administration of hyaluronic acid and salts thereof.

[0020] It is another object of the instant invention to provide novel chondroprotective/restorative compositions.

[0021] A further object of the invention is to provide a novel chondroprotective/restorative composition containing hyaluronic acid in paste or gel form.

[0022] A still further object of the invention is to provide novel chondroprotective/restorative compositions containing hyaluronic acid, glucosamine sulfate and chondroitin sulfate.

[0023] An additional object of the invention is to provide chondroprotective/restorative compositions containing hyaluronic acid and bioeffective materials.

[0024] A still additional object of the invention is to provide chondroprotective/restorative compositions containing hyaluronic acid, vitamins and minerals.

[0025] An additional object of the present invention is provide chondroprotective/restorative compositions containing hyaluronic acid, vitamins and minerals.

[0026] Another main object of the present invention is to provide an aqueous gel containing hyaluronic acid and molasses.

[0027] Another object of the present invention is to provide paste formulations containing hyaluronic acid, glucosamine sulfate and molasses.

[0028] An additional object of the invention is to provide gel formulations containing HA in a carboxymethylcellulose base.

[0029] A further object of the invention is to provide animal feeds containing hyaluronic acid.

[0030] These and other objects of the invention will become apparent from the description hereinafter.

SUMMARY OF THE INVENTION

[0031] The present invention provides a method for treating or preventing osteoarthritis, joint effusion, joint inflammation and pain, synovitis, lameness, post operative arthroscopic surgery, deterioration of proper joint function, the reduction or inhibition of metabolic activity of chondrocytes, the activity of enzymes that degrade cartilage, the reduction or inhibition of the production of hyaluronic acid, said method comprising orally administering to a mammalian species a therapeutically effective amount of hyaluronic acid or pharmaceutically acceptable salts thereof.

[0032] The invention is also directed to a Chondroprotective/Restorative composition comprising Hyaluronic Acid or its pharmaceutically acceptable salts and optionally a pharmaceutically acceptable carrier.

[0033] The instant invention also provides a Chondroprotective/Restorative composition comprising: (a) an effective amount of Glucosamine sulfate; (b) an effective amount Hyaluronic Acid or pharmaceutically acceptable salts thereof; and (c) optionally a pharmaceutically acceptable carrier.

[0034] Additionally, the invention provides a Chondroprotective/Restorative composition comprising: (b) an effective amount of Chondroitin sulfate; (b) an effective amount of Hyaluronic Acid or pharmaceutically acceptable salts thereof; and (c) optionally a pharmaceutically acceptable carrier.

[0035] The instant invention further provides a Chondroprotective/Restorative composition comprising: (a) an effective amount of Glucosamine sulfate; (b) an effective amount of Chondroitin sulfate; (c) an effective amount of Hyaluronic Acid or pharmaceutically acceptable salts thereof; and (d) optionally a pharmaceutically acceptable carrier.

[0036] The Chondroprotective/Restorative compositions of the invention further include nutritionally effective amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof.

[0037] The invention is also directed to an animal feed having Chondroprotective/Restorative benefits comprising: (a) a nutritionally effective feed base selected from the group consisting of grains, proteins and fats; and (b) an effective amount of Hyaluronic Acid or pharmaceutically acceptable salts thereof.

[0038] Furthermore, the invention relates to a therapeutic Chondroprotective/Restorative composition comprising: (a) Hyaluronic Acid or its pharmaceutically acceptable salts; (b) a therapeutic drug; and (c) optionally a pharmaceutically acceptable carrier.

[0039] The invention is also directed to a Chondroprotective/Restorative composition in paste form comprising: (a) an effective amount of Hyaluronic Acid or its pharmaceutically acceptable salts; and (b) a sufficient amount of molasses to make a paste.

[0040] Additionally, the invention also relates to a Chondroprotective/Restorative composition in gel form comprising: (a) an effective amount of Hyaluronic Acid or its pharmaceutically acceptable salts; and (b) a sufficient amount of carboxymethylcellulose to make a paste.

DETAILED DESCRIPTION OF INVENTION

[0041] In the first preferred embodiment of the invention, there is provided viscosupplementation of joints by oral administration of sodium hyaluronate (HA) to mammals and more in particular to racing thoroughbreds. Applicant's conducted a double blind placebo-controlled study wherein ten horses were randomly chosen and given an oral gel (also known as Conquer and containing 100 mg of hyaluronic acid) for 59 days. Every parameter used to measure soundness was improved in the HA treated group. Also, every parameter used to measure routine maintenance of the racing Thoroughbred was improved in the HA treated group. All horses in the treated group with pre-existing conditions showed clinical improvement during the study.

[0042] In conducting our study, ten actively training Thoroughbreds were randomly selected. Five were given a placebo gel and five were given a gel containing 100 mg of Sodium Hyaluronate. The duration of the study was 59 days. The ages of the horses varied: one two-year old, five three-year olds, two four-year olds, and two five-year olds. Because the half-life of circulating HA is two days or less, the horses were given 100 mg once daily. Upon completion of the study, training and veterinary records were evaluated. Number of days to the track was compared to number of days walked. In addition, horses receiving NSAIDS during the study for any reason were recorded as were horses examined for any lameness. Horses were evaluated weekly for joint effusion, pain on flexion, and signs of lameness. Horses radiographed due to lameness were recorded. Horses with pre-existing conditions were monitored and periodically evaluated.

[0043] The results of oral administration of HA are listed in Tables 1 and 2 below. Treated horses went to the track more days than the non-treated group (40 versus 32). Horse 110, of the non-treated group sustained a cortical stress fracture 33 days into the study. With this non-articular injury removed from the study, the average days to the track of the non-treated group changes from 32 to 35 days. All of the non-treated horses were examined for lameness at some time during the study. None of the treated horses were examined for lameness. All horses in the treated group with pre-existing conditions improved. NSAIDS, primarily phenylbutazone, was used at some time during the study in 5 of 5 of the non-treated horses. Less was used in the treated group, 2 of 5. None of the treated group were radiographed during the study while 3 of 5 of the non-treated group had radiographs taken. More horses developed new signs of synovial effusion in the non-treated group, 3 of 5, than in the treated group, 1 of 5. The treated group required less bandaging (3 of 5) than the non-treated group (5 of 5).

TABLE 1

Horses	Age	Sex	Days To Track	Days Walked	Examined For Lameness	NSAIDS	Radiographed
TREATED HORSES							
101	5	G	45	14	NO	YES	NO
102	2	F	41	18	NO	NO	NO

TABLE 1-continued

Horses	Age	Sex	Days To Track	Days Walked	Examined For Lameness	NSAIDS	Radiographed
105	4	M	38	21	NO	NO	NO
106	5	M	31	28	NO	NO	NO
109	4	M	46	13	NO	YES	NO
			TREATED TOTALS				
N/A	N/A	N/A	201 (Ave. 40)	94 (Ave. 19)	NONE	2/5	NONE
			NON-TREATED HORSES				
103	3	C	44	15	YES	YES	NO
104	3	C	19	40	YES	YES	YES
107	3	F	43	16	YES	YES	NO
108	3	C	34	25	YES	YES	YES
110*	3	C	19	40	YES	YES	YES
			NON-TREATED TOTALS				
N/A	N/A	N/A	159 (Ave. 32)	136 (Ave. 27)	5/5	5/5	3/5

*Horse 110 sustained a cortical stress fracture 33 days into the study. By removing him from the totals the average days to the track becomes 35 days instead of 32 days.

[0044]

TABLE 2

Horse	Pre-existing Condition	Condition	Improved	New Joint Effusion During Study	Location
		TREATED HORSES			
101	YES	Osslets	YES	NO	N/A
102	NO	N/A	N/A	YES	CARPUS
105	YES	Severe T Sheath Eff.	YES	NO	N/A
106	YES	Chronic Osslets	YES	NO	N/A
109	YES	Osslets	YES	NO	N/A
		NON-TREATED HORSES			
103	YES	Stiffness Behind	YES	YES	Carpus
104	NO	N/A	N/A	NO	N/A
107	NO	N/A	N/A	YES	Fetlocks
108	YES	Left Front Soreness	NO	YES	Stifles
110	NO	N/A	N/A	NO	N/A

[0045] As can be appreciated from Tables 1 and 2, horses maintained on a daily dose of oral sodium hyaluronate showed improvement of all soundness characteristics measured. Horses with pre-existing synovitis improved while on oral HA. Accordingly, the data suggests that Oral sodium hyaluronate appears to be effective in preventing lameness in the racing Thoroughbred. None of the horses in the treated group were examined for lameness while in the non-treated group, two horses developed mild forelimb lameness which were subtle and difficult to diagnose with diagnostic nerve blocks, one horse became painful in his back and front feet and a fourth horse became acutely lame after a race. This lameness could not be completely diagnosed with nerve blocks therefore a bone scan was performed. Results showed increased uptake in the left carpus, left front fetlock, and solar margins of the foot. After resting about 30 days, this horse resumed training. The present invention provides evidence of HA's ability to have a performance enhancing effect in the racing Thoroughbred when used orally. In addition, oral administration of HA is effective in the treatment of synovitis associated with osteoarthritis.

[0046] In the second preferred embodiment of the invention, an oral preparation containing sodium hyaluronate was evaluated in the treatment of aseptic synovitis. Horses chosen had clinical signs of joint disease and were treated with 100 mg of Sodium Hyaluronate, 1 g Chondroitin sulfate, and 200 mg Vitamin C for 30 days.

[0047] In conducting the above study, six adult horses were administered 100 mg of sodium hyaluronate, 1 g of Chondroitin sulfate, and 200 mg Vitamin C daily in an oral preparation. The horses were treated for 30 days and were monitored continuously. Clinical evaluations were performed on day 1, day 30, and at day 45 (two weeks after discontinuation of treatment). Clinically, four horses had significant aseptic syovitis of the metacarpolphalangeal joints. One horse suffered from villinodular synovitis and one horse had degenerative joint disease of the proximal interphalangeal joint (ringbone). The results of the study are summarized in Table 3 below.

TABLE 3

Symptom	Day 1	Day 30	Day 45
Overall evaluation	Inflammed effusion Pain on flexion	Improved in 5 of 6 horses	Improved in 5 of 6 horses
Swelling effusion	6 of 6 horses	Improved in 5 of 6 horses	Improved in 5 of 6 horses
Joint Pain	6 of 6 horses	Improved in 5 of 6 horses	Improved in 5 of 6 horses
Lameness	Grade 3 or 2 lame in 6 of 6 horses	Sound in 5 of 6 horses	Sound in 5 of 6 horses
Range of Motion	Decreased in 6 of 6 horses	Improved in 5 of 6 horses	Improved in 5 of 6 horses

[0048] As can be appreciated from Table 3, significant improvement was seen in five of six horses. The amount of synovial effusion and inflammation decreased in all but one case. There was improvement of lameness and decreased pain on flexion. The horse diagnosed with degenerative joint disease of the proximal interphalangeal joint showed no improvement. Oral delivery of sodium hyaluronate is a viable alternative for treatment of synovitis in the horse. It is very safe with no side effects being reported in this study.

[0049] In a third embodiment of the invention, another oral gel consisting of 100 mg per dose of sodium hyaluronate was evaluated. Horses chosen had significant signs of synovitis and joint pain. Treatment was continued for 21 days. In conducting the study, four weanling Thoroughbred foals and one three year old Thoroughbred racehorse were given 100 mg daily of sodium hyaluronate in a gel formulation. All horses were diagnosed with moderate to severe synovitis of the metacarpolphalangeal joints. Two of the foals and the three year old racehorse had moderate to severe effusion and pain in both fore fetlocks while the other two had marked synovitis of all four fetlocks. Three of the foals were Grade 1/5 lame and one foal was grade 2/5 lame at a walk and trot. The race horse was not lame at a walk or trot but was painful on flexion. All foals were very painful on

flexion and lameness was significantly worsened following fetlock flexion tests. Radiographs of the affected fetlocks did not reveal any bony abnormalities. Treatment was continued for 21 days and all horses wee evaluated weekly. No other treatments were administered during this time.

[0050] The results are summarized in Table 4. In one foal with effusion in all four fetlocks (Grade 1/5 lame), significant improvement was seen after seven days of treatment. Synovial effusion had decreased and the foal was sound at a walk and trot. Slight lameness was observed after fetlock flexion. By week two, this foal's joints were considered normal and no pain on flexion or lameness could be detected. In the second foal with marked effusion in all four fetlocks (Grade 2/5 lame), moderate synovial effusion was still present at seven days. After fetlock flexion, this foal's lameness worsened to a Grade 4/5. At the 14th day exam, significant improvement was observed. The amount of joint swelling had decreased dramatically and the foal's lameness was improved. There was lameness pain on flexion and the lameness after fetlock flexion improved to a Grade 1/5. At the 21st day exam, the joints were considered normal and the foal was sound at a walk and trot. The third and fourth foals with synovial effusion in the front fetlocks showed significant improvement in seven days. They continued to have slight pain on flexion and slightly lame after fetlock flexion. By 14 days these foals had slight effusion but were sound and negative to fetlock flexion. At the 21st day exam they were considered normal. The 3 year old racehorse had a significant decrease in synovitis at day 7. By the 14th day there was slight effusion and no pain on flexion. At 21 days, there continued to be slight effusion but no lameness or pain on flexion.

TABLE 4

Horse	Day 1	Day 7	Day 14	Day 21
#1	Moderate effusion in all four fetlocks. Grade 1/5 lame/ Moderate pain on flexion	Mild effusion in all four fetlock/Sound/Slight pain on flexion	No effusion. Sound/ No pain on flexion	No effusion. Sound/No pain on flexion
#2	Severe effusion in all four Fetlocks Grade 2/5 lame, Severe pain on flexion	Moderate effusion in all four fetlocks. Grade 1/5 lame fetlocks. Moderate pain on flexion	Mild effusion in front Grade 1/5 lame Moderate pain on flexion	Slight effusion in front fetlocks, Sound, Slight pain on flexion
#3	Moderate effusion on front Fetlocks. Grade 1/5 lame, Mild pain on flexion	Mild effusion in front Fetlocks. Sound, Mild pain on flexion	Slight effusion in front Fetlock. Sound, No pain on flexion	No effusion, Sound No pain on flexion
#4	Moderate effusion on front Fetlocks. Grade 1/5 lame, Mild pain on flexion	Mild effusion in front Fetlocks. Sound, Mild pain on flexion	Slight effusion in front Fetlock. Sound, No pain on flexion	No effusion, Sound No pain on flexion
#5*	Moderate effusion in front Fetlocks. No Lameness, Mild pain on flexion	Mild effusion in front Fetlocks. Sound, slight pain on flexion	Slight effusion in front Fetlock. Sound, No pain on flexion	No effusion, Sound No pain on flexion

*Three year old racehorse

[0051] In a further clinical trial of the invention, 24 hockey players were treated via oral administration with a combination of sodium hyaluronate and chondroitin sulphate in gel form as exemplified in Example 16 for three months. The dosage levels were 0.1–0.5 mg/Kg of body weight. A greater than sixty five percent improvement in their knee joint was observed.

[0052] Additionally, 27 human patients were treated via oral administration with a combination of sodium hyaluronate and chondroitin sulphate in gel form as exemplified in Example 16 for three months after knee surgery. The dosage levels were 0.1–0.5 mg/Kg of body weight. At least a 58% improvement was observed on their knee joints.

[0053] It should be noted that in treating mammals the recommended daily dosage for hyaluronic acid is about 0.1 to 0.5 mg/Kg of body weight. Accordingly, for a human the dosage ranges can be from 7 to 40 mg, while for a horse the range can be from 50-250 mg and for a dog the ranges would be 2-8 mg.

[0054] In a fourth embodiment, the invention also provides chondroprotective and restorative compositions which are very useful for oral administration. The compositions contain 10 to 2000 mg of hyaluronic acid and optionally a pharmaceutically acceptable carrier.

[0055] In a fifth embodiment, the present invention relates to chondroprotective and restorative compositions useful for oral administration containing: (a) 0.01-10 wt % hyaluronic acid or its pharmaceutical acceptable salts; (b) optionally 20-60 wt % glucosamine or its pharmaceutically acceptable salts; (c) optionally 1-15 wt % chondroitin or its pharmaceutical acceptable salts; (d) optionally nutritionally effective (recommended daily allowance) amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, B complex, B12, B1, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof; (e) optionally effective amounts of a bioactive agent or drug; and (f) optionally a pharmaceutically or nutritionally acceptable carrier.

[0056] The pharmaceutical acceptable salts of hyaluronic acid include the alkali metal salts as well as the alkaline earth metal salts. Typical salts include sodium hyaluronate, potassium hyaluronate, magnesium hyaluronate and calcium hyaluronate. The preferred salt in the compositions of the invention is sodium hyaluronate.

[0057] The pharmaceutically effective salts of glucosamine are selected from the group consisting of glucosamine chloride, glucosamine bromide, glucosamine iodide and glucosamine sulfate. Similarly, with chondroitin the same type of salts are usable i.e., chondroitin chloride, chondroitin bromide, chondroitin sulfate and chondroitin iodide.

[0058] The bio-effective or drug component of the invention is selected from the group consisting of angiotensin converting enzyme inhibitors, anti-asthmatics, anti-cholesterolemics, anti-convulsants, anti-depressants, anti-diarrhea preparations, anti-infectives, anti-inflammatory agents, anti-nauseants, anti-stroke agents, anti-tumor drugs, anti-tussives, anti-uricemic drugs, amino-acid preparations, anti-emetics, antiobesity drugs, antiparasitics, antipyretics, appetite stimulants, cerebral dilators, chelating agents, cholecystokinin antagonists, cognition activators, deodorants, dermatological agents, diabetes agents, diuretics, erythropoietic drugs, fertility agents, synthetic hormones, laxatives, mineral supplements, neuroleptics, neuromuscular agents, peripheral vaso-dilators, prostaglandins, vaginal preparations, vaso-constrictors and vertigo agents.

[0059] The bio-effecting agent is selected from the group consisting of acetaminophen, acetic acid, acetylsalicylic acid, buffered acetylsalicylic acid, albuterol, albuterol sulfate, ethanol isopropanol, allantoin, aloe, aluminum acetate, aluminum carbonate, aluminum chlorohydrate, aluminum hydroxide, alprozolam, amino acids, aminobenzoic acid, amoxicillin, ampicillin, amsacrine, amsalog, anethole, aspartame, atenolol, bacitracin, balsam peru, beclomethasone dipropionate, benzocaine, benzoic acid, benzophenones, benzoyl peroxide, biotin, bisacodyl, bornyl acetate, bromopheniramine maleate, buspirone, caffeine, calamine, calcium, calcium carbonate, calcium casinate, calcium hydroxide, camphor, captopril, cascara sagrada, castor oil, Cephalosporins, cefaclor, cefadroxil, cephalexin, cetylalcohol, cetylpyridinium chloride, chelated minerals, chloramphenicol, chlorcyclizine hydrochloride, chlorhexidine gluconate, chloroxylenol, chloropentostatin, chlorpheniramine maleate, cholestyramine resin, choline bitartrate, cimetidine hydrochloride, cinnamedrine hydrochloride, citalopram, citric acid, Clenbuterol, cocoa butter, cod liver oil, codeine and codeine phosphate, clonidine, clonidine hydrochloride, clorfibrate, ciprofloxacin HCl, cyanocobalamin, cyclizine hydrochloride, DMSO, danthron, Dantrium, dexamethazone, dexbrompheniramine maleate, dextromethorphan hydrobromide, diazapam, dibucaine, diclofenac sodium, digoxin, diltiazem, dimethicone, dioxybenzone, diphenhydramine citrate, diphenhydramine hydrochloride, docusate calcium, docusate potassium, docusate sodium, doxycycline hyclate, doxylamine succinate, efaroxan, enalapril, enoxacin, erythromycin, estropipate, ethinyl estradiol, ephedrine, epinephrine bitartrate, erythropoietin, eucalyptol, ferrous fumarate, ferrous gluconate, ferrous sulfate, folic acid, fosphenytoin, Flunixin Meglumine, fluoxetine HCl, furosemide, gabapentan, gentamicin, Gentocin sulfate, gemfibrozil, glipizide, glycerin, glyceryl stearate, griseofulvin, guaifenesin, hexylresorcinol, hydrochlorothiaxide, hydrocodone bitartrate, hydrocortisone, hydrocortisone acetate, 8-hydroxyquinoline sulfate, ibuprofen, indomethacin, inositol, insulin, iodine, ipecac, iron, isoxicam, ketamine, Ketofin, koalin, lactic acid, lanolin, lecithin, lidocaine, lidocaine hydrochloride, lifinopril, liotrix, lovastatin, MSM (methylsulfonylmethane), magnesium carbonate, magnesium hydroxide, magnesium salicylate, magnesium trisilocate, mefenamic acid, meclofenanic acid, meclofenamate sodium, medroxyprogesterone acetate, methenamine mandelate, Methocarbamol, menthol, meperidine hydrochloride, metaproterenol sulfate, methyl nicotinate, methyl salicylate, methylcellulose, methsuximide, metromidazole, metromidazole hydrochloride, metoprolol tartrate, miconazole nitrate, mineral oil, minoxidil, morphine, naproxen, naproxen sodium, nifedipine, neomycin sulfate, Neomycin-Bacitracin, niacin, niacinamide, nicotine, nicotinamide, nitroglycerin, nonoxynol-9, norethindone, norethindone acetate, nystatin, octoxynol, octyl dimethyl PABA, octyl methoxycinnamate, omega-3 polyunsaturated fatty acids, omeprazole, oxolinic acid, oxybenzone, oxtriphylline, para-aminobenzoic acid (PABA), padimate O, paramethadione, Penicillin, pentastatin, peppermint oil, pentaerythriol tetranitrate, pentobarbital sodium, pheniramine maleate, phenobarbital, phenol, phenolphthalein, phenybutazone, phenylephrine hydrochloride, phenylpropanolamine, phenylpropanolamine hydrochloride, phenytoin, phenelzine sulfate, pirmenol, piroxicam, polymycin B sulfate, potassium chloride, potassium nitrate, prazepam, prednisone, prednisolone, procainamide hydrochloride, procaterol, propoxyphene, propoxyphene HCl, propoxyphene napsylate, pramiracetin, pramoxine, pramoxine hydrochloride, propronolol HCl, pseudoephedrine hydrochloride, pseudoephedrine sulfate, pyridoxine, quinapril, quinidine gluconate, quinestrol, ralitoline, ranitadine, resorcinol, riboflavin, salicylic acid, sesame oil, shark liver oil, simethicone, sodium bicarbonate, sodium citrate, sodium fluoride, sodium monofluorophosphate, Sulfa-drugs, sulfanethoxazole, sulfur, tacrine, tacrine HCl, theophylline, terfenidine, thioperidone, trimetrexate, triazolam, timolol maleate, tretinoin, tetracycline hydrochloride, tolmetin, tolnaftate, triamcinilone, triclosan, triprolidine hydrochloride, undecylenic acid, vancomycin, verapamil HCl, vidaribine phosphate, vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, vitamin K, witch hazel, xylometazoline hydrochloride, zinc, zinc sulfate, and zinc undecylenate.

[0060] The compositions of the invention can be made in paste form, gel forms, tablets and capsules. The paste form of the invention contains molasses in an amount effective to form a paste.

[0061] The gel forms of the invention are formed by mixing the actives with water and then adding a gelling agent. The gelling agent is selected from the group consisting of cellulose or a cellulose derivative in an amount of from 0.5 to 5 wt. % and said cellulose derivative is selected from the group consisting of hydroxypropyl methyl cellulose, hydroxymethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, cellulose acetate, ethyl cellulose, methyl hydroxy ethyl cellulose, hydroxy ethyl cellulose, cellulose gum carboxymethylcellulose and sodium carboxymethylcellulose.

[0062] In making the compositions of the invention, the active materials will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

[0063] Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, manni-

tol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, methylcelluse, methyl and propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions may be formulated so as to provide rapid, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well-know in the art.

[0064] In a sixth embodiment of the invention, an animal feed is provided having chondroprotective and restorative properties. The animal feed base of the present invention comprises farinaceous material selected from the group consisting of wheat, wheat flour, wheat meal by-products and corn in an amount of 25 to 70% by weight based on the total weight of the feed, further comprising proteinaceous material selected from the group consisting of soybean meal, soy flour, peanut meal, cottonseed meal, safflower seed meal in an amount of from 5 to 40% by weight based on the total weight of the feed, further comprising fibrous material selected from the group consisting of soy hulls, cottonseed hulls, rice hulls in an amount of from about 2 to 35% by weight based on the total weight of the feed, further comprising nutritional supplements selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof, in an amount of from 3 to 4% by weight based on the total weight of the feed, further comprising a vegetable oil coating, said oil selected from the group consisting of soybean oil, corn oil, safflower oil, cottonseed oil, peanut oil, in an amount of from 1 to 15% by weight based on the total weight of the feed.

[0065] The above feed base is blended with a paste having the following formulation ranges: (a) 0.01-10 wt % hyaluronic acid or its pharmaceutical acceptable salts; (b) optionally 20-60 wt % glucosamine or its pharmaceutically acceptable salts; (c) optionally 1-15 wt % chondroitin or its pharmaceutical acceptable salts; (d) optionally nutritionally effective (recommended daily allowance) amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, B complex, B12, B1, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof; (e) optionally effective amounts of a bioactive agent or drug; and (f) 15-35 wt % molasses. The feed of course is formulated in way to provide optimum nutrition and optimum chondroprotection depending on the specific animal and their current state of health.

[0066] The present invention is the most unique chondoprotectice/restorative agent available. The molasses flavored oral paste provides a practical, efficient, and effective means of administration orally or top dressing feed. When added to the feed, the molasses base binds to the feed to insure total consumption. When necessary, an easy measurable dose can be administered orally. The highly palatable formulation of the invention is the first to combine high levels of Glucosamine sulfate (GS) with Chondroitin sulfate (CS) and Hyaluronic Acid (HA) in an easy to absorb, low molecular weight formula. It has also been shown that liquid or paste forms are more readily absorbed than encapsulated or powder forms. The chondroprotective/restorative agent of the invention enhance chondrocyte synthesis, increase synthesis of hyaluronic acid, inhibit enzymes that degrade cartilage, and reduce pain and synovitis. It must also slow down or reverse progression of the disease. The present invention, with it's unique combination of GS, CS, and HA is the closest yet to satisfying these criteria.

[0067] These three substances are the three connective tissue molecules needed to rebuild and synthesize new tissue. Connective tissue is mainly of collagen and proteoglycans. Proteoglycans provide the framework for collagen and hold water, enhancing the flexibility and resistance to compression needed to counteract physical stress. The building blocks for all proteglycans are amino sugars. Glucosamine is the building block needed as the precursor for all subsequent amino sugar synthesis. The formation of N-acetylglucosamine, chondroitin sulfate, and hyaluronic acid require glucosamine for their synthesis. In fact, glucosamine makes up 50% of the hyaluronic acid molecule.

[0068] Glucosamine sulfate along with Chondroitin sulfate have become very popular supplements administered in the treatment of degenerative joint disease. Recent studies have questioned whether the combination produces better results than Glucosamine sulfate alone. Also there is much debate over which glucosamine salt is preferred. Embodiments of the present invention utilize Glucosamine sulfate as it's source of Glucosamine. Most of the past and present research has been performed on the sulfated form. There is evidence that suggests that a component of the activity of GS and CS is related to the sulfate residues found in these compounds. Sulfur is an essential nutrient for the stabilization of the connective tissue matrix. It has been proposed that the sulfate molecules of GS and CS contribute to the therapeutic benefits of the compounds in generative joint disease. If this is true, it would suggest that GS, as opposed to N-acetylglucosamine and glucosamine HCl, is the best form of glucosamine supplementation. Recently, it has been shown that high-dose glucosamine may provide rapid symptomatic benefit and in the longer term and the repair of damaged cartilage. The high dose of glucosamine non only promotes synthesis of cartilage proteogycans, but stimulates synovial production of hyaluronic acid. This would explain the anecdotal reports that a high dose of glucosamine is beneficial.

[0069] As previously explained, the present invention comprises a highly palatable formulation, which is the first to combine high levels of Glucosamine sulfate (GS) with Chondroitin sulfate (CS) and Hyaluronic Acid (HA) in an easy to absorb, low molecular weight formula.

[0070] Glucosamine, which is formed in the body as glucosamine 6-phosphate is the most fundamental building block required for the biosynthesis of the classes of compounds such as glucolipids, glycoproteins, glycosaminoglycans, hyaluronate, and proteoglycans. Directly or indirectly, glucosamine plays a role in the formation of articular surfaces, tendons, ligaments, synovial fluid, skin, bone, heart valves, blood vessels and mucus secretions of the digestive, respiratory and urinary tracts. Glucosamine sulfate is greater than 90% absorbed and is quickly incorporated into articular cartilage following oral administration.

[0071] In one study, no LD50 was established for Glucosamine sulfate since even at very high levels (5000 mg/kg

orally) there was no mortality in mice and rats. While treatment with GC does not produce the initial dramatic reductions in pain normally associated with NSAIDs, it's ability to reduce pain is consistent and progressive throughout the course of it's administration, resulting in a long-term improvement in the condition. Glucosamine is a small molecule and is very soluble in water.

[0072] Chondroitin Sulfate achieves benefits much more slowly than glucosamine. Chondroitin bioavailability following oral administration is around 15%. Because of its lower availability, the time needed to see a clinical response is lengthened. Chondroitin improves joint fluidity by drawing water to the cartilage tissue. When this water is drawn into the cartilage, it is accompanied by nutrients which are supplied to the cartilage. Additionally Chondroitin helps fight enzymes that inhibit transportation of nutrients into these tissues as it prevents other enzymes from tearing down cartilage tissue. Furthermore, Chondroitin, like Glucosamine, promotes the product of key cartilage components such as proteoglycans and it also prevents abnormal cell death.

[0073] Hyaluronic acid is one of many glycosaminoglycans of physiological significance. Other are Chondroitin sulfate, Heparin sulfate, and Dermatan sulfate. The HA molecule is very similar to that of Chondroitin sulfate. In numerous studies, the oral absorption of CS, HS and DS have been well documented. The bioavailabilities range from 15-20%. Hyaluronic acid has been shown to be absorbed through skin and reach the dermal lymphatics. Also, high levels of hyaluronan has been detected in the intestinal lymphatics. In addition, studies have been performed to determine the effects of HA secreted in saliva. Others have looked at hyaluronic acid production by oral epithelial cells. According to the present invention, there is a beneficial effect when Glucosamine sulfate, Chondroitin sulfate, and Hyaluronic acid are administered orally. Generally, the oral administration of embodiments of the present composition has a quicker clinical response than is produced when each component of the composition is given individually. A significant difference is an acute or a rapid relief in join pain inflammation and swelling achieved by oral administration of the composition. A dramatic improvement over seven to ten days is achieved whereas it usually takes weeks for that effect to occur. Another benefit received is that of oral preparation and administration of the HA given, for example, in the equine in any formulation. The administration of the HA composition orally and having a clinical effect eliminates more evasive procedures. Other ways to give HA would be more evasive, such an injection by IV or other administration into the joints. Basically, the embodiments of the present invention include oral preparations that are less evasive and also may include an embodiment which is the only oral way to give HA. This provides another alternative to giving it by an injection.

[0074] Another benefit is that embodiments of the present invention, with it's high dose of Glucosamine sulfate, Hyaluronic acid, and Chondroitin sulfate, appears to have a synergistic effect which hastens the clinical response.

[0075] One further embodiment of the present invention is a unique formulation that combines Glucosamine sulfate, Chondroitin sulfate, and Hyaluronic acid into a paste formulation for direct oral administration or top dressing feed. This is the only product available which combines these three substances which are critical for cartilage metabolism and production of synovial fluid. Also, this embodiment is the only oral paste formulation available for any one of these supplements. Early clinical trials have shown that when the three products are combined, they have a synergistic effect. The clinical effects have been impressive. Data has shown a quicker clinical response when GS, CS, and HA are combined than when they are used individually. Conditions in which embodiments of the present invention would be beneficial:

[0076] 1) Osteoarthritis

[0077] 2) Joint effusion

[0078] 3) Joint inflammation and pain

[0079] 4) Post operative arthroscopic surgery

[0080] 5) Restoring proper joint function

[0081] 6) Promote metabolic activity of chondrocytes (cartilage producing cells)

[0082] 7) Inhibit enzymes that degrade cartilage

[0083] 8) Stimulate the production of Hyaluronic acid.

[0084] Embodiments of the present invention possess the following advantages:

[0085] 1) Only paste formulation

[0086] 2) Only combination of GS, CS, HA in a paste formulation

[0087] 3) Only oral paste form of Glucosamine

[0088] 4) Only oral paste form of Chondroitin

[0089] 5) Only oral paste form of Hyaluronic acid

[0090] 6) Only oral paste in a molasses flavored base

[0091] 7) Only oral gel in apple flavored carboxymethylcellulose base.

[0092] One embodiment of the present invention possesses a molasses flavor. Other flavors would include apple, cherry, and any other palatable flavor. One embodiment of the present invention comprises the following:

	Wt %
Glucosamine sulfate	46.03
Chondroitin sulfate	4.60
Sodium Hyaluronate	0.18
Manganese sulfate	0.18
Powdered sugar	8.70
Xanthan gum	0.10
Molasses	25.00
Water	14.00
Glycerine	0.70
Corn Starch	0.30
Sodium Benzoate	0.50

[0093] Embodiments of the present invention in a paste formulation has many advantages. When adding to feed, the formulation will stick to grain to insure total consumption. Embodiments of the past formulation can be given orally (direct administration) or added to feed-depending on man-

agement of animals (turned our in field vs. stall confinement). Other advantages include the following:

[0094] 1) Better absorption with liquids

[0095] 2) Molasses flavored paste—more palatable

[0096] 3) Apple flavored gel—more palatable

[0097] 3) Sticky consistency—animal cannot spit product from mouth which insures total dose

[0098] 4) Syringe dose insures more accurate dose.

[0099] 5) Brown sugar included—more palatable Effects of GS vs CS: Glucosamine sulfate:

[0100] 1) Enhances chondrocyte synthesis

[0101] 2) Enhances synthesis of hyaluronic acid

[0102] 3) Reduces joint pain

[0103] 4) Reduces synovitis Chondroitin sulfate:

[0104] 1) Also helps with chondrocyte synthesis

[0105] 2) CS has been found to inhibit degradative enzymes in cartilage

[0106] 3) CS strengthens and enhances vessels that feed joints or supply them with nutrients by reducing arterial plaque and clear cholesterol deposits.

[0107] 4) Reduces joint pain and improves joint mobility.

[0108] 5) Reduces synovitis associated with joint arthritis.

[0109] Neither GS or CS fulfills the quest for the ideal chondroprotective/restorative agent separately but when combined they appear to provide the necessary components for the health and wellbeing of the joint. Hyaluronic acid complements the combination by helping to restore the HA levels needed for joint health and lubrication which are decreased when synovitis is present.

[0110] Hyaluronic acid is a glycosaminoglycan. Other glycosaminoglycans are Chondroiting sulfate, Heparin sulfate, and Dermatan sulfate. The most abundant GAG is Chondroitin sulfate. The three related GAGs have been found to be absorbed orally. Because of their chemical similarities and the clinical reports of improvement of synovitis, HA has a syunergistic effect with GS and CS when given orally. This effect is observed as a more rapid clinical response than then GS and CS are given individually.

[0111] Clinically, responses are seen in 7 to 10 days vs three to four weeks or not at all when GS and CS are given without HA. Therefore, we have seen a dramatic decrease in synovitis when HA is combined with GS and CS. This leads us to conclude that HA is absorbed orally and effective either alone or in combination with GS and CS. Therefore, an additional embodiment of the invention comprises a composition including HA and any acceptable carrier, such as the paste formulation disclosed herein and any other liquid, powder, gel or similar type carrier.

[0112] Another embodiment of the invention includes a paste formulation containing the active component isoxuprine. Isoxuprine is a vasodilator and is utilized in treatment of many afflictions including the treatment of navicular disease. One effect of isoxuprine is that it stimulates the vasodilator nerves, such as the vaso-inhibitory and vasohypotonic nerves, and causes dilation or relaxation of the blood vessels. Administration of isoxuprine to a patient, such as an animal, in the form of a paste is beneficial to ensure adequate administration.

[0113] The present invention is illustrated by the following Examples, but should not be construed to be limited thereto. In the Examples, "part" and "%" are all part by weight or % by weight unless specified otherwise. Examples 1-14 are paste compositions of the invention.

EXAMPLE 1

Component	Wt %
Sodium Hyaluronate	0.144
Powdered Sugar 10X	60.144
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

EXAMPLE 2

Component	Wt %
Chondroitin Sulfate	4
Sodium Hyaluronate	0.144
Powdered Sugar 10X	50.144
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	29.5
Water DI	14.4
TOTAL	100

EXAMPLE 3

Component	Wt %
Glucosamine Sulfate	40.144
Sodium Hyaluronate	0.144
Powdered Sugar 10X	20
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

EXAMPLE 4

Component	Wt %
Glucosamine Sulfate	36.144
Chondroitin Sulfate	4
Sodium Hyaluronate	0.144
Powdered Sugar 10X	20
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

-continued

EXAMPLE 5

Component	Wt %
Glucosamine Sulfate	36
Sodium Hyaluronate	0.144
Manganese Sulfate	0.144
Powdered Sugar 10X	24
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

EXAMPLE 6

Component	Wt %
Chondroitin Sulfate	4
Sodium Hyaluronate	0.144
Manganese Sulfate	0.144
Powdered Sugar 10X	56
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

EXAMPLE 7

Component	Wt %
Glucosamine Sulfate	36
Chondroitin Sulfate	4
Sodium Hyaluronate	0.144
Manganese Sulfate	0.144
Powdered Sugar 10X	20
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

EXAMPLE 8

Component	Wt %
Glucosamine Sulfate	35
Chondroitin Sulfate	4
Sodium Hyaluronate	0.144
Manganese Sulfate	0.144
Vitamin C	1
Powdered Sugar 10X	20
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

-continued

EXAMPLE 9

Component	Wt %
Glucosamine Sulfate	36
Chondroitin Sulfate	4
Sodium Hyaluronate	0.144
Manganese Sulfate	0.144
Vitamin D	200 IU
Powdered Sugar 10X	20
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

EXAMPLE 10

Component	Wt %
Glucosamine Sulfate	36
Chondroitin Sulfate	4
Sodium Hyaluronate	0.144
Manganese Sulfate	0.144
Ibuprofen	200 mg
Powdered Sugar 10X	20
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

EXAMPLE 11

Component	Wt %
Glucosamine Sulfate	36
Chondroitin Sulfate	4
Sodium Hyaluronate	0.144
Manganese Sulfate	0.144
Erythromycin	300 mg
Powdered Sugar 10X	20
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

EXAMPLE 12

Component	Wt %
Glucosamine Sulfate	36
Chondroitin Sulfate	4
Sodium Hyaluronate	0.144
Manganese Sulfate	0.144
Isoxuprine	100 mg
Powdered Sugar 10X	20
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

-continued

EXAMPLE 13

Component	Wt %
Glucosamine Sulfate	40.344
Sodium Hyaluronate	0.344
Ibuprofen	800 mg
Powdered Sugar 10X	20
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

EXAMPLE 14

Component	Wt %
Glucosamine Sulfate	46.03
Chondroitin Sulfate	4.60
Sodium Hyaluronate	0.18
Manganese Sulfate	0.18
Powdered Sugar 10X	8.70
Glycerine	5.7
Xanthan Gum	0.10
Sodium Benzoate	0.50
Corn Starch	0.30
Molasses	25.00
Water DI	14.0
TOTAL	100

EXAMPLE 15

[0114] The following Example is directed to a gel of HA using CMC as the gelling agent.

Component	Wt %
Sodium Hyaluronate	1.00
Sodium Carboxymethyl cellulose	1.00
Propylene glycol	1.20
Sodium Benzoate	0.50
Citric Acid	0.30
Apple Flavor	1.5
Water DI	94.5
TOTAL	100

EXAMPLE 16

[0115] The following Example is directed to a gel of HA and chondroitin sulphate using CMC as the gelling agent.

Component	Wt %
Sodium Hyaluronate	1.00
Chondroitin Sulphate	4.00
Sodium Carboxymethyl cellulose	1.00
Propylene glycol	1.20
Sodium Benzoate	0.50

-continued

Component	Wt %
Citric Acid	0.30
Apple Flavor	1.5
Water DI	90.5
TOTAL	100

EXAMPLE 16

[0116] Hard gelatin capsules are prepared using the following ingredients

Component	Amount mg
Sodium Hyaluronate	100.00
Starch dried	200.00
Magnesium stearate	10.00
TOTAL	310.00

EXAMPLE 17

[0117] Hard gelatin capsules are prepared using the following ingredients

Component	Amount mg
Sodium Hyaluronate	100.00
Chondroitin sulphate	200.00
Starch dried	200.00
Magnesium stearate	10.00
TOTAL	510.00

[0118] The above ingredients are mixed and filled into hard gelatin capsules in 510 mg quantities.

EXAMPLE 18

[0119] Hard gelatin capsules are prepared using the following ingredients

Component	Amount mg
Sodium Hyaluronate	100.00
Microcrystalline cellulose	400.00
Silicon Dioxide, fumed	10.00
Stearic Acid	5.00
TOTAL	310.00

[0120] The components are blended and compressed to form tablets each weighing 665 mg.

[0121] While the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications, and variations will be apparent to those skilled in the art in light of the foregoing description. Accordingly, it is intended to embrace all such

alternatives, modifications, and variations which fall within the spirit and broad scope of the invention.

What we claim is:

1. A method of treating or preventing osteoarthritis, joint effusion, joint inflammation and pain, synovitis, lameness, post operative arthroscopic surgery, deterioration of proper joint function, the reduction or inhibition of metabolic activity of chondrocytes, the activity of enzymes that degrade cartilage, the reduction or inhibition of the production of Hyaluronic acid in a mammal, said method comprising orally administering to said mammal a therapeutically effective amount of Hyaluronic Acid or pharmaceutically acceptable salts thereof.

2. The method of claim 1 further including an effective amount of Glucosamine or its pharmaceutically acceptable salts.

3. The method of claim 1 further including an effective amount of chondroitin or its pharmaceutically acceptable salts.

4. The method of claim 2 wherein said pharmaceutically acceptable salt is glucosamine sulfate.

5. The method of claim 3 wherein said pharmaceutically acceptable salt is chondroitin sulfate.

6. The method of claim 1 further including therapeutically effective amounts of glucosamine sulfate and chondroitin sulfate.

7. The method according to claim 1 wherein said hyaluronic acid is uncrosslinked.

8. The method according to claim 1 wherein said pharmaceutically acceptable salt is sodium hyaluronate.

9. The method according to claim 8 wherein said therapeutically effective amount of sodium hyaluronate is in the range of 10 mg to 2000 mg.

10. A Chondroprotective/Restorative composition comprising an effective amount Hyaluronic Acid or its pharmaceutically acceptable salts and optionally a pharmaceutically acceptable carrier.

11. A Chondroprotective/Restorative composition comprising:

(a) an effective amount of Glucosamine sulfate;

(b) an effective amount Hyaluronic Acid or pharmaceutically acceptable salts thereof; and

(c) optionally a pharmaceutically acceptable carrier.

12. A Chondroprotective/Restorative composition comprising:

(b) an effective amount of Chondroitin sulfate;

(b) an effective amount of Hyaluronic Acid or pharmaceutically acceptable salts thereof; and (c) optionally a pharmaceutically acceptable carrier.

13. A Chondroprotective/Restorative composition comprising

(a) an effective amount of Glucosamine sulfate;

(b) an effective amount of Chondroitin sulfate;

(c) an effective amount of Hyaluronic Acid or pharmaceutically acceptable salts thereof; and (d) optionally a pharmaceutically acceptable carrier.

14. The Chondroprotective/Restorative composition of claim 10 further including nutritionally effective amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof.

15. The Chondroprotective/Restorative composition of claim 11 further including nutritionally effective amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof.

16. The Chondroprotective/Restorative composition of claim 12 further including nutritionally effective amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof.

17. The Chondroprotective/Restorative composition of claim 13 further including nutritionally effective amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof.

18. An animal feed having Chondroprotective/Restorative benefits comprising:

(a) a nutritionally effective feed base selected from the group consisting of grains, proteins, fats and mixtures thereof; and

(b) an effective amount of Hyaluronic Acid or pharmaceutically acceptable salts thereof.

19. The animal feed of claim 18 further including an effective amount of Glucosamine sulfate.

20. The animal feed of claim 19 further including an effective amount of Chondroitin sulfate.

21. The animal feed of claim 20 further including molasses.

22. The animal feed of claim 21 further including nutritionally effective amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof.

23. The animal feed of claim 22 in the form of a paste.

24. The animal feed according to claim 23, which is a cat feed.

25. The animal feed according to claim 23, which is a dog feed.

26. The animal feed according to claim 23, which is a horse feed.

27. A therapeutic and Chondroprotective/Restorative composition comprising:

(a) an effective amount of hyaluronic Acid or its pharmaceutically acceptable salts;

(b) an effective amount of a therapeutic drug; and

(c) optionally a pharmaceutically acceptable carrier.

28. The therapeutic and Chondroprotective/Restorative composition of claim 27 wherein said therapeutic drug is selected from the group consisting of acetaminophen, acetic acid, acetylsalicylic acid, buffered acetylsalicylic acid, albuterol, albuterol sulfate, ethanol isopropanol, allantoin, aloe, aluminum acetate, aluminum carbonate, aluminum

chlorohydrate, aluminum hydroxide, alprozolam, amino acids, aminobenzoic acid, amoxicillin, ampicillin, amsacrine, amsalog, anethole, aspartame, atenolol, bacitracin, balsam peru, beclomethasone dipropionate, benzocaine, benzoic acid, benzophenones, benzoyl peroxide, biotin, bisacodyl, bornyl acetate, brompheniramine maleate, buspirone, caffeine, calamine, calcium, calcium carbonate, calcium casinate, calcium hydroxide, camphor, captopril, cascara sagrada, castor oil, Cephalosporins, cefaclor, cefadroxil, cephalexin, cetylalcohol, cetylpyridinium chloride, chelated minerals, chloramphenicol, chlorcyclizine hydrochloride, chlorhexidine gluconate, chloroxylenol, chloropentostatin, chlorpheniramine maleate, cholestyramine resin, choline bitartrate, cimetidine hydrochloride, cinnamedrine hydrochloride, citalopram, citric acid, Clenbuterol, cocoa butter, cod liver oil, codeine and codeine phosphate, clonidine, clonidine hydrochloride, clorfibrate, ciprofloxacin HCl, cyanocobalamin, cyclizine hydrochloride, DMSO, danthron, Dantrium, dexamethazone, dexbrompheniramine maleate, dextromethorphan hydrobromide, diazapam, dibucaine, diclofenac sodium, digoxin, diltiazem, dimethicone, dioxybenzone, diphenhydramine citrate, diphenhydramine hydrochloride, docusate calicum, docusate potassium, docusate sodium, doxycycline hyclate, doxylamine succinate, efaroxan, enalapril, enoxacin, erythromycin, estropipate, ethinyl estradiol, ephedrine, epinephrine bitartrate, erythropoietin, eucalyptol, ferrous fumarate, ferrous gluconate, ferrous sulfate, folic acid, fosphenytoin, Flunixin Meglumine, fluoxetine HCl, furosemide, gabapentan, gentamicin, Gentocin sulfate, gemfibrozil, glipizide, glycerin, glyceryl stearate, griseofulvin, guaifenesin, hexylresorcinol, hydrochlorothiaxide, hydrocodone bitartrate, hydrocortisone, hydrocortisone acetate, 8-hydroxyquinoline sulfate, ibuprofen, indomethacin, inositol, insulin, iodine, ipecac, iron, isoxicam, Isoxuprine, ketamine, Ketofin, koalin, lactic acid, lanolin, lecithin, lidocaine, lidocaine hydrochloride, lifinopril, liotrix, lovastatin, MSM (methylsulfonylmethane), magnesium carbonate, magnesium hydroxide, magnesium salicylate, magnesium trisilocate, mefenamic acid, meclofenanic acid, meclofenamate sodium, medroxyprogesterone acetate, methenamine, mandelate, Methocarbamol, menthol, meperidine hydrochloride, metaproterenol sulfate, methyl nicotinate, methyl salicylate, methylcellulose, methsuximide, metromidazole, metromidazole hydrochloride, metoprolol tartrate, miconazole nitrate, mineral oil, minoxidil, morphine, naproxen, naproxen sodium, nifedipine, neomycin sulfate, Neomycin-Bacitracin, niacin, niacinamide, nicotine, nicotinamide, nitroglycerin, nonoxynol-9, norethindone, norethindone acetate, nystatin, octoxynol, octyl dimethyl PABA, octyl methoxycinnamate, omega-3 polyunsaturated fatty acids, omeprazole, oxolinic acid, oxybenzone, oxtriphylline, para-aminobenzoic acid (PABA), padimate O, paramethadione, Penicillin, pentastatin, peppermint oil, pentaerythriol tetranitrate, pentobarbital sodium, pheniramine maleate, phenobarbital, phenol, phenolphthalein, phenybutazone, phenylephrine hydrochloride, phenylpropanolamine, phenylpropanolamine hydrochloride, phenytoin, phenelzine sulfate, pirmenol, piroxicam, polymycin B sulfate, potassium chloride, potassium nitrate, prazepam, prednisone, prednisolone, procainamide hydrochloride, procaterol, propoxyphene, propoxyphene HCl, propoxyphene napsylate, pramiracetin, pramoxine, pramoxine hydrochloride, propronolol HCl, pseudoephedrine hydrochloride, pseudoephedrine sulfate, pyridoxine, quinapril, quinidine gluconate, quinestrol, ralitoline, ranitadine, resorcinol, riboflavin, salicylic acid, sesame oil, shark liver oil, simethicone, sodium bicarbonate, sodium citrate, sodium fluoride, sodium monofluorophosphate, Sulfa-drugs, sulfamethoxazole, sulfur, tacrine, tacrine HCl, theophylline, terfenidine, thioperidone, trimetrexate, triazolam, timolol maleate, tretinoin, tetracycline hydrochloride, tolmetin, tolnaftate, triamcinolone, triclosan, triprolidine hydrochloride, undecylenic acid, vancomycin, verapamil HCl, vidaribine phosphate, vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, vitamin K, witch hazel, xylometazoline hydrochloride, zinc, zinc sulfate, and zinc undecylenate.

29. A Chondroprotective/Restorative composition in paste form comprising:

(a) an effective amount of Hyaluronic Acid or its pharmaceutically acceptable salts; and

(b) a sufficient amount of molasses to make a paste.

30. The Chondroprotective/Restorative composition of claim 29 further including glucosamine sulfate.

31. The Chondroprotective/Restorative composition of claim 30 further including chondroitin sulfate.

32. The Chondroprotective/Restorative composition of claim 31 further including nutritionally effective amounts of vitamins and minerals.

33. A method of enhancing chondrocyte synthesis in a mammal which method comprises administering orally to said mammal an effective amount of the composition according to claim 31.

34. A method for inhibiting enzymes that degrade cartilage, and reduce pain and synovitis in a mammal which method comprises administering orally to said mammal an effective amount of the composition according to claim 31.

35. A Chondroprotective/Restorative composition in gel form comprising:

(a) an effective amount of Hyaluronic Acid or its pharmaceutically acceptable salts;

(b) water; and

(c) a sufficient amount of carboxymethylcellulose or its sodium salt to make a gel.

36. The Chondroprotective/Restorative composition of claim 35 further including glucosamine sulfate.

37. The Chondroprotective/Restorative composition of claim 35 further including chondroitin sulfate.

38. The Chondroprotective/Restorative composition of claim 35 further including nutritionally effective amounts of vitamins and minerals.

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(12) **United States Patent**
Pierce

(10) **Patent No.: US 6,924,273 B2**
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(54) **CHONDROPROTECTIVE/RESTORATIVE COMPOSITIONS AND METHODS OF USE THEREOF**

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(58) **Field of Search** 514/54, 62, 2, 514/56; 424/423, 134.1, 450, 484, 756, 499, 548, 639, 486, 488; 536/21, 54, 18.7, 55.1, 55.2

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(57) **ABSTRACT**

The instant invention provides a method of treating or preventing osteoarthritis, joint effusion, joint inflammation and pain, synovitis, lameness, post operative arthroscopic surgery, deterioration of proper joint function including joint mobility, the reduction or inhibition of metabolic activity of chondrocytes, the activity of enzymes that degrade cartilage, the reduction or inhibition of the production of Hyaluronic acid, said method comprising orally administering to a mammalian species a therapeutically effective amount of Hyaluronic Acid or pharmaceutically acceptable salts thereof. Additionally, compositions containing hyaluronic acid; chondroitin sulfate, and glucosamine sulfate in a paste formulation are also disclosed which can be administered on their own or can be used as a feed additive.

28 Claims, No Drawings

CHONDROPROTECTIVE/RESTORATIVE COMPOSITIONS AND METHODS OF USE THEREOF

This application claims benefit of application Ser. No. 60/237,838 filed Oct. 03, 2000.

FIELD OF INVENTION

The present invention relates to medically useful preparations based on hyaluronic acid and pharmaceutically acceptable salts thereof, a naturally-occurring substance found in animal tissue, and especially in rooster comb, vitreous humour, umbilical cords, and synovial fluid of mammals. This invention also relates to new orally administrable formulations containing hyaluronic acid. The instant invention is also directed to chondroprotective/restorative compositions containing hyaluronic acid. This invention also relates to new pharmaceutical formulations containing hyaluronic acid. The invention is further directed to a new veterinary formulations containing hyaluronic acid. This invention further relates to orally administrable veterinary formulation containing hyaluronic acid.

The present invention is also directed to veterinary formulations containing hyaluronic acid and additional bioeffective active ingredients such as bioactive agents useful in the treatment of domesticated animals especially horses. This invention also provides methods for treating horses in need of chondroprotection. The invention is further directed to pharmaceutical compositions containing hyaluronic acid, glucosamine and chondroitin. The present invention also relates to a method of treating aseptic synovitis in horses with hyaluronic acid atone or in combination with other active ingredients. More specifically, the present invention is also intended for therapeutic treatments of arthritis and related conditions using pharmaceutical compositions containing hyaluronic acid as well as other active ingredients effective in the treatment of joint diseases. The compositions of the invention are particularly useful in the veterinary field but are also very useful in treatment of humans.

This invention further relates to the oral administration of forms of hyaluronic acid and pharmaceutically acceptable salts thereof such as sodium hyaluronate, and orally administrable dosage forms containing forms of hyaluronic acid, for the prevention and/or treatment of diseases such as osteoarthritis, joint effusion, joint inflammation and pain, synovitis, and many other diseases associated with cartilage degeneration.

The instant invention also provides gels of hyaluronic acid with carboxymethylcellulose.

BACKGROUND OF THE INVENTION

Hyaluronic acid (HA) exists as a naturally-occurring polysaccharide (also known as a mucoid polysaccharide) that can be extracted from such diverse sources as rooster comb, umbilical cord, vitreous humor, synovial fluid, pathologic joints, skin and group A and C hemolytic Streptococci. The hyaluronic acid is also defined as a high viscosity naturally occurring glycosaminoglycan having a polymeric structure containing alternating N-acetyl-D-glucosamine and D-glucuronic acid monosaccharide units linked with β 1–4 bonds and the disaccharide units linked with β 1–3 glycoside bonds. It occurs usually as the sodium salt and has a molecular weight range of about 50,000 to 8×10^6 Daltons.

Hyaluronic acid is a naturally occurring glycosaminoglycan. HA is ubiquitous in the organism, with the highest concentration found in soft connective tissue and joint fluid.

It is a constituent of the intercellular matrix of connective tissue that exists in almost all vertebrates. It plays an important role in a number of physiological functions, including protection and lubrication of cells, maintenance of the structural integrity of tissues, transport of molecules and cells, cell migration, cell function and differentiation, and fluid retention and regulation. The clinical benefits of intra-articular HA in the horse are well published.

Natural Hyaluronic acid is polydisperse in respect of molecular weight and is known to show excellent biocompatibility even when implanted or injected into the body by virtue of the absence of species and organ specificity. However, because of the relatively short in vivo residence time of Hyaluronic acid solution in biological applications, improvements in the persistency of Hyaluronic acid by chemical crosslinking with various chemical modifiers has been attempted to broaden its use for medical materials.

The isolation and characterization of Hyaluronic acid is described in Meyer et al, J. Biol. Chem. 107, 629 (1934); J. Biol. Chem. 114, 689 (1936); Balazs, Fed. Proc. 17, 1086 (1958); Laurent et al; Biochim. Biophys. Acta 42, 476 (1960). The structure of Hyaluronic acid was elucidated by Weissman et al, J. Am. Chem. Soc. 76, 1753 (1954) and Meyer, Fed. Proc. 17, 1075 (1958).

Hyaluronic acid is an important component of the intercellular matrix. Specifically, the highest levels are found in the eye and synovial fluid of joints. In joints, its primary role is that of lubrication, reducing pain, and inflammation. In arthritic joints HA is deficient. In healthy joints, synovial fluid supplies nutrition to the articular cartilage and has incomparable functions as a lubricant and as a shock absorber. It has been determined that its excellent viscoelastisity owes heavily to one of the main components, present therein, Hyaluronic acid. Concentration and molecular weight analyses of Hyaluronic acid demonstrated the concentration and molecular weight of Hyaluronic acid in the synovial fluid from patients with arthritis such as osteoarthritis and chronic articular rheumatism generally tended to be lower than in normal synovial fluid, and the lower concentration and molecular weight of Hyaluronic acid were closely associated with development of locomotor dysfunction and pain attributable to the weaker lubricating action and the weaker protecting action on the surface of the articular cartilage of synovial fluid.

Degradation of the structures in articular cartilage is a typical characteristic of all diseases resulting in chronic destruction of the joint structures. Examples of such disorders are rheumatoid arthritis, psoriatic arthritis, and osteoarthrosis. Also, acute inflammation of a joint is often accompanied by destruction of the cartilage, although in most cases this will not develop into the chronically destructive disease. It is not known which factors are crucial for the acutely inflamed joint to either proceed to healing or develop into the chronic process. Examples of diseases involving acute joint inflammation are yersinia arthritis, pyrophosphate arthritis, gout arthritis (arthritis urica), septic arthritis and various forms of arthritis of traumatic etiology. Among other factors potentially conducive to the destruction of articular cartilage may be mentioned, for instance, treatment with cortisone; this has been known for a long time to accelerate the degenerative process in osteoarthrosis.

Such a so-called "steroid arthropathy" occurs far too often as an undesirable side effect of intra-articular cortisone treatment and can be avoided only by providing for a sufficiently long period of rest after the treatment. Steroid arthropathy is characterized by an advanced degree of

articular destruction and X-ray-detectable changes of the same type as occur in advanced degenerative articular disease (Nizolek, D H & White, K K, Cornell Vet. 1981, 71:355–75). According to what is at present accepted as an explanation of the degenerative arthropathy development following treatment with cortisone, this arthropathy is believed to be caused by a primary effect on the chondrocyte metabolism. It should be noted, however, that the actual conditions prevailing in cases of arthritis with severe inflammation of the joint are of a rather more complex character, since in those cases injection of cortisone appears to have an overall positive effect on the clinical picture.

Also, it is well known that articular cartilage is composed of about 70% of water, chondrocytes and a cartilage matrix. The major components constituting the articular matrix are collagen and proteoglycan; the proteoglycan having good water retention characteristics is contained in the network of collagen having a reticulated structure. The articular matrix is rich in viscoelasticity and has an important role in reducing the stimulus and load imposed on the cartilage in order to maintain the normal morphology and function of the articular cartilage.

Osteoarthritis and rheumatoid arthritis are representative of the diseases accompanied by the destruction of the cartilage matrix. It is thought that the destruction of the matrix in these diseases is triggered by mechanical stresses with aging in the case of osteoarthritis and by excess proliferation of the surface layer cells of the synovial membrane, pannus formation and inflammatory cell infiltration in the case of rheumatoid arthritis, and both phenomena are caused through the induction of proteases. Since the degradation of articular cartilage is progressed in the extracellular region at a neutral pH, it is said that a matrix metalloprotease (hereinafter referred to as "MMP" or "MMPs" when used as the general term) whose optimal pH is in the neutral range plays a leading role in the degradation.

No medical cure exists for osteoarthritis. The progressive degeneration of the joint due to osteoarthritis is irreversible. Present therapies are directed to palliative medical therapies to reduce inflammation and pain and surgical therapies to reconstruct an affected joint or, in severe cases, to replace the joint with an artificial, prosthetic joint.

Injection of high molecular weight Hyaluronic acid solution into diseased joints has been widely adopted as an effective measure for osteoarthritis among those articular diseases, and the source of high purity HA preparations for this purpose is cockscombs. Such HA preparations from cockscombs are biologically inherent and quite safe but usually have to be administered as frequently as several to 10 times to show significant therapeutic effect. Persistency tests on rabbits revealed that HA with a molecular weight of less than 1000000 administered into the knee joint cavities disappeared from the knee joint cavities in 1 to 3 days and suggested the need of frequent administrations (Blood Coagulation and Fibrinolysis, vol, 2(1): 173–8, (1991)).

On the other hand, the molecular weight of HA found in the living body is reported to be as high as millions to 10000000, and a crosslinked HA derivative obtained by treatment with a chemical crosslinker has been developed as a therapeutic agent for knee joints with the idea that high molecular weight HA closer to the biologically intact one is likely to have higher effect. Reportedly, the crosslinked HA persisted for a period as long as 20 to 30 days after administration into rabbit knee joint cavities in the above-mentioned persistency tests and produced sufficient effect when administered three times in clinical tests, and is practically used as a therapeutic agent for arthritis (see Blood Coagulation and Fibrinolysis, ibid.; and Journal of Rheumatology vol. 25(9): 1813–9 (1998)).

A need exists for an effective palliative medication for the treatment of osteoarthritis and other joint diseases which is both safe and effective when used for both short-term and long-term therapy and which can be administered orally.

OBJECTS OF THE INVENTION

It is a first object of the present invention to provide a method for treating mammals having joint diseases by oral administration of hyaluronic acid and salts thereof.

It is another object of the instant invention to provide novel chondroprotective/restorative compositions.

A further object of the invention is to provide a novel chondroprotective/restorative composition containing hyaluronic acid in paste or gel form.

A still further object of the invention is to provide novel chondroprotective/restorative compositions containing hyaluronic acid, glucosamine sulfate and chondroitin sulfate.

An additional object of the invention is to provide chondroprotective/restorative compositions containing hyaluronic acid and bioeffective materials.

A still additional object of the invention is to provide chondroprotective/restorative compositions containing hyaluronic acid, vitamins and minerals.

An additional object of the present invention is provide chondroprotective/restorative compositions containing hyaluronic acid, vitamins and minerals.

Another main object of the present invention is to provide an aqueous gel containing hyaluronic acid and molasses.

Another object of the present invention is to provide paste formulations containing hyaluronic acid, glucosamine sulfate and molasses.

An additional object of the invention is to provide gel formulations containing HA in a carboxymethylcellulose base.

A further object of the invention is to provide animal feeds containing hyaluronic acid.

These and other objects of the invention will become apparent from the description hereinafter.

SUMMARY OF THE INVENTION

The present invention provides a method for treating or preventing osteoarthritis, joint effusion, joint inflammation and pain, synovitis, lameness, post operative arthroscopic surgery, deterioration of proper joint function, the reduction or inhibition of metabolic activity of chondrocytes, the activity of enzymes that degrade cartilage, the reduction or inhibition of the production of hyaluronic acid, said method comprising orally administering to a mammalian species a therapeutically effective amount of hyaluronic acid or pharmaceutically acceptable salts thereof.

The invention is also directed to a Chondroprotective/Restorative composition comprising Hyaluronic Acid or its pharmaceutically acceptable salts and optionally a pharmaceutically acceptable carrier.

The instant invention also provides a Chondroprotective/Restorative composition comprising: (a) an effective amount of Glucosamine sulfate; (b) an effective amount Hyaluronic Acid or pharmaceutically acceptable salts thereof; and (c) optionally a pharmaceutically acceptable carrier.

Additionally, the invention provides a Chondroprotective/Restorative composition comprising: (b) an effective

amount of Chondroitin sulfate; (b) an effective amount of Hyaluronic Acid or pharmaceutically acceptable salts thereof; and (c) optionally a pharmaceutically acceptable carrier.

The instant invention further provides a Chondroprotective/Restorative composition comprising: (a) an effective amount of Glucosamine sulfate; (b) an effective amount of Chondroitin sulfate; (c) an effective amount of Hyaluronic Acid or pharmaceutically acceptable salts thereof; and (d) optionally a pharmaceutically acceptable carrier.

The Chondroprotective/Restorative compositions of the invention further include nutritionally effective amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof.

The invention is also directed to an animal feed having Chondroprotective/Restorative benefits comprising: (a) a nutritionally effective feed base selected from the group consisting of grains, proteins and fats; and (b) an effective amount of Hyaluronic Acid or pharmaceutically acceptable salts thereof.

Furthermore, the invention relates to a therapeutic Chondroprotective/Restorative composition comprising: (a) Hyaluronic Acid or its pharmaceutically acceptable salts; (b) a therapeutic drug; and (c) optionally a pharmaceutically acceptable carrier.

The invention is also directed to a Chondroprotective/Restorative composition in paste form comprising: (a) an effective amount of Hyaluronic Acid or its pharmaceutically acceptable salts; and (b) a sufficient amount of molasses to make a paste.

Additionally, the invention also relates to a Chondroprotective/Restorative composition in gel form comprising: (a) an effective amount of Hyaluronic Acid or its pharmaceutically acceptable salts; and (b) a sufficient amount of carboxymethylcellulose to make a paste.

DETAILED DESCRIPTION OF INVENTION

In the first preferred embodiment of the invention, there is provided viscosupplementation of joints by oral administration of sodium hyaluronate (HA) to mammals and more in particular to racing thoroughbreds. Applicant's conducted a double blind placebo-controlled study wherein ten horses were randomly chosen and given an oral gel (also known as Conquer and containing 100 mg of hyaluronic acid) for 59 days. Every parameter used to measure soundness was improved in the HA treated group. Also, every parameter used to measure routine maintenance of the racing Thoroughbred was improved in the HA treated group. All horses in the treated group with pre-existing conditions showed clinical improvement during the study.

In conducting our study, ten actively training Thoroughbreds were randomly selected. Five were given a placebo gel and five were given a gel containing 100 mg of Sodium Hyaluronate. The duration of the study was 59 days. The ages of the horses varied: one two-year old, five three-year olds, two four-year olds, and two five-year olds. Because the half-life of circulating HA is two days or less, the horses were given 100 mg once daily. Upon completion of the study, training and veterinary records were evaluated. Number of days to the track was compared to number of days walked. In addition, horses receiving NSAIDS during the study for any reason were recorded as were horses examined for any lameness. Horses were evaluated weekly for joint effusion, pain on flexion, and signs of lameness. Horses radiographed due to lameness were recorded. Horses with pre-existing conditions were monitored and periodically evaluated.

The results of oral administration of HA are listed in Tables 1 and 2 below. Treated horses went to the track more days than the non-treated group (40 versus 32). Horse 110, of the non-treated group sustained a cortical stress fracture 33 days into the study. With this non-articular injury removed from the study, the average days to the track of the non-treated group changes from 32 to 35 days. All of the non-treated horses were examined for lameness at some time during the study. None of the treated horses were examined for lameness. All horses in the treated group with pre-existing conditions improved. NSAIDS, primarily phenylbutazone, was used at some time during the study in 5 of 5 of the non-treated horses. Less was used in the treated group, 2 of 5. None of the treated group were radiographed during the study while 3 of 5 of the non-treated group had radiographs taken. More horses developed new signs of synovial effusion in the non-treated group, 3 of 5, than in the treated group, 1 of 5. The treated group required less bandaging (3 of 5) than the non-treated group (5 of 5).

TABLE 1

Horses	Age	Sex	Days To Track	Days Walked	Examined For Lameness	NSAIDS	Radiographed
TREATED HORSES							
101	5	G	45	14	NO	YES	NO
102	2	F	41	18	NO	NO	NO
105	4	M	38	21	NO	NO	NO
106	5	M	31	28	NO	NO	NO
109	4	M	46	13	NO	YES	NO
TREATED TOTALS							
N/A	N/A	N/A	201 (Ave. 40)	94 (Ave. 19)	NONE	2/5	NONE
NON-TREATED HORSES							
103	3	C	44	15	YES	YES	NO
104	3	C	19	40	YES	YES	YES
107	3	F	43	16	YES	YES	NO
108	3	C	34	25	YES	YES	YES
110*	3	C	19	40	YES	YES	YES
NON-TREATED TOTALS							
N/A	N/A	N/A	159 (Ave. 32)	136 (Ave. 27)	5/5	5/5	3/5

*Horse 110 sustained a cortical stress fracture 33 days into the study. By removing him from the totals the average days to the track becomes 35 days instead of 32 days.

TABLE 2

Horse	Pre-existing Condition	Condition	Improved	New Joint Effusion During Study	Location
TREATED HORSES					
101	YES	Osslets	YES	NO	N/A
102	NO	N/A	N/A	YES	CARPUS
105	YES	Severe T Sheath Eff.	YES	NO	N/A

TABLE 2-continued

Horse	Pre-existing Condition	Condition	Improved	New Joint Effusion During Study	Location
106	YES	Chronic Osslets	YES	NO	N/A
109	YES	Osslets	YES	NO	N/A
		NON-TREATED HORSES			
103	YES	Stiffness Behind	YES	YES	Carpus
104	NO	N/A	N/A	NO	N/A
107	NO	N/A	N/A	YES	Fetlocks
108	YES	Left Front Soreness	NO	YES	Stifles
110	NO	N/A	N/A	NO	N/A

As can be appreciated from Tables 1 and 2, horses maintained on a daily dose of oral sodium hyaluronate showed improvement of all soundness characteristics measured. Horses with pre-existing synovitis improved while on oral HA. Accordingly, the data suggests that Oral sodium hyaluronate appears to be effective in preventing lameness in the racing Thoroughbred. None of the horses in the treated group were examined for lameness while in the non-treated group, two horses developed mild forelimb lameness which were subtle and difficult to diagnose with diagnostic nerve blocks, one horse became painful in his back and front feet and a fourth horse became acutely lame after a race. This lameness could not be completely diagnosed with nerve blocks therefore a bone scan was performed. Results showed increased uptake in the left carpus, left front fetlock, and solar margins of the foot. After resting about 30 days, this horse resumed training. The present invention provides evidence of HA's ability to have a performance enhancing effect in the racing Thoroughbred when used orally. In addition, oral administration of HA is effective in the treatment of synovitis associated with osteoarthritis.

In the second preferred embodiment of the invention, an oral preparation containing sodium hyaluronate was evaluated in the treatment of aseptic synovitis. Horses chosen had clinical signs of joint disease and were treated with 100 mg of Sodium Hyaluronate, 1 g Chondroitin sulfate, and 200 mg Vitamin C for 30 days.

In conducting the above study, six adult horses were administered 100 mg of sodium hyaluronate, 1 g of Chondroitin sulfate, and 200 mg Vitamin C daily in an oral preparation. The horses were treated for 30 days and were monitored continuously. Clinical evaluations were performed on day 1, day 30, and at day 45 (two weeks after discontinuation of treatment). Clinically, four horses had significant aseptic syovitis of the metacarpolphalangeal joints. One horse suffered from villinodular synovitis and one horse had degenerative joint disease of the proximal interphalangeal joint (ringbone). The results of the study are summarized in Table 3 below.

TABLE 3

Symptom	Day 1	Day 30	Day 45
Overall evaluation	Inflammed effusion Pain on flexion	Improved in 5 of 6 horses	Improved in 5 of 6 horses
Swelling effusion	6 of 6 horses	Improved in 5 of 6 horses	Improved in 5 of 6 horses
Joint Pain	6 of 6 horses	Improved in 5 of 6 horses	Improved in 5 of 6 horses

TABLE 3-continued

Symptom	Day 1	Day 30	Day 45
Lameness	Grade 1 or 2 lame in 6 of 6 horses	Sound in 5 of 6 horses	Sound in 5 of 6 horses
Range of Motion	Decreased in 6 of 6 horses	Improved in 5 of 6 horses	Improved in 5 of 6 horses

As can be appreciated from Table 3, significant improvement was seen in five of six horses. The amount of synovial effusion and inflammation decreased in all but one case. There was improvement of lameness and decreased pain on flexion. The horse diagnosed with degenerative joint disease of the proximal interphalangeal joint showed no improvement. Oral delivery of sodium hyaluronate is a viable alternative for treatment of synovitis in the horse. It is very safe with no side effects being reported in this study.

In a third embodiment of the invention, another oral gel consisting of 100 mg per dose of sodium hyaluronate was evaluated. Horses chosen had significant signs of synovitis and joint pain. Treatment was continued for 21 days. In conducting the study, four weanling Thoroughbred foals and one three year old Thoroughbred racehorse were given 100 mg daily of sodium hyaluronate in a gel formulation. All horses were diagnosed with moderate to severe synovitis of the metacarpolphalangeal joints. Two of the foals and the three year old racehorse had moderate to severe effusion and pain in both fore fetlocks while the other two had marked synovitis of all four fetlocks. Three of the foals were Grade 1/5 lame and one foal was grade 2/5 lame at a walk and trot. The race horse was not lame at a walk or trot but was painful on flexion. All foals were very painful on flexion and lameness was significantly worsened following fetlock flexion tests. Radiographs of the affected fetlocks did not reveal any bony abnormalities. Treatment was continued for 21 days and all horses wee evaluated weekly. No other treatments were administered during this time.

The results are summarized in Table 4. In one foal with effusion in all four fetlocks (Grade 1/5 lame), significant improvement was seen after seven days of treatment. Synovial effusion had decreased and the foal was sound at a walk and trot. Slight lameness was observed after fetlock flexion. By week two, this foal's joints were considered normal and no pain on flexion or lameness could be detected. In the second foal with marked effusion in all four fetlocks (Grade 2/5 lame), moderate synovial effusion was still present at seven days. After fetlock flexion, this foal's lameness worsened to a Grade 4/5. At the 14th day exam, significant improvement was observed. The amount of joint swelling had decreased dramatically and the foal's lameness was improved. There was lameness pain on flexion and the lameness after fetlock flexion improved to a Grade 1/5. At the 21st day exam, the joints were considered normal and the foal was sound at a walk and trot. The third and fourth foals with synovial effusion in the front fetlocks showed significant improvement in seven days. They continued to have slight pain on flexion and slightly lame after fetlock flexion. By 14 days these foals had slight effusion but were sound and negative to fetlock flexion. At the 21st day exam they were considered normal. The 3 year old racehorse had a significant decrease in synovitis at day 7. By the 14th day there was slight effusion and no pain on flexion. At 21 days, there continued to be slight effusion but no lameness or pain on flexion.

TABLE 4

Horse	Day 1	Day 7	Day 14	Day 21
#1	Moderate effusion in all four fetlocks. Grade 1/5 lame/ Moderate pain on flexion	Mild effusion in all four fetlock/Sound/Slight pain on flexion	No effusion. Sound/ No pain on flexion	No effusion. Sound/No pain on flexion
#2	Severe effusion in all four Fetlocks Grade 2/5 lame, Severe pain on flexion	Moderate effusion in all four fetlocks. Grade 1/5 lame fetlocks. Moderate pain on flexion	Mild effusion in front Grade 1/5 lame Moderate pain on flexion	Slight effusion in front fetlocks, Sound, Slight pain on flexion
#3	Moderate effusion on front Fetlocks. Grade 1/5 lame, Mild pain on flexion	Mild effusion in front Fetlocks. Sound, Mild pain on flexion	Slight effusion in front Fetlock. Sound, No pain on flexion	No effusion, Sound No pain on flexion
#4	Moderate effusion on front Fetlocks. Grade 1/5 lame, Mild pain on flexion	Mild effusion in front Fetlocks. Sound, Mild pain on flexion	Slight effusion in front Fetlock. Sound, No pain on flexion	No effusion, Sound No pain on flexion
#5*	Moderate effusion in front Fetlocks. No Lameness, Mild pain on flexion	Mild effusion in front Fetlocks. Sound, slight pain on flexion	Slight effusion in front Fetlock. Sound, No pain on flexion	No effusion, Sound No pain on flexion

*Three year old racehorse

In a further clinical trial of the invention, 24 hockey players were treated via oral administration with a combination of sodium hyaluronate and chondroitin sulphate in gel form as exemplified in Example 16 for three months. The dosage levels were 0.1–0.5 mg/Kg of body weight. A greater than sixty five percent improvement in their knee joint was observed.

Additionally, 27 human patients were treated via oral administration with a combination of sodium hyaluronate and chondroitin sulphate in gel form as exemplified in Example 16 for three months after knee surgery. The dosage levels were 0.1–0.5 mg/Kg of body weight. At least a 58% improvement was observed on their knee joints.

It should be noted that in treating mammals the recommended daily dosage for hyaluronic acid is about 0.1 to 0.5 mg/Kg of body weight. Accordingly, for a human the dosage ranges can be from 7 to 40 mg; while for a horse the range can be from 50–250 mg and for a dog the ranges would be 2–8 mg.

In a fourth embodiment, the invention also provides chondroprotective and restorative compositions which are very useful for oral administration. The compositions contain 10 to 2000 mg of hyaluronic acid and optionally a pharmaceutically acceptable carrier.

In a fifth embodiment, the present invention relates to chondroprotective and restorative compositions useful for oral administration containing: (a) 0.01–10 wt % hyaluronic acid or its pharmaceutical acceptable salts; (b) optionally 20–60 wt % glucosamine or its pharmaceutically acceptable salts; (c) optionally 1–15 wt % chondroitin or its pharmaceutical acceptable salts; (d) optionally nutritionally effective (recommended daily allowance) amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, B complex, B12, B1, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof; (e) optionally effective amounts of a bioactive agent or drug; and (f) optionally a pharmaceutically or nutritionally acceptable carrier.

The pharmaceutical acceptable salts of hyaluronic acid include the alkali metal salts as well as the alkaline earth metal salts. Typical salts include sodium hyaluronate, potassium hyaluronate, magnesium hyaluronate and calcium hyaluronate. The preferred salt in the compositions of the invention is sodium hyaluronate.

The pharmaceutically effective salts of glucosamine are selected from the group consisting of glucosamine chloride, glucosamine bromide, glucosamine iodide and glucosamine sulfate. Similarly, with chondroitin the same type of salts are usable i.e., chondroitin chloride, chondroitin bromide, chondroitin sulfate and chondroitin iodide.

The bio-effective or drug component of the invention is selected from the group consisting of angiotensin converting enzyme inhibitors, anti-asthmatics, anti-cholesterolemics, anti-convulsants, anti-depressants, anti-diarrhea preparations, anti-infectives, anti-inflammatory agents, anti-nauseants, anti-stroke agents, anti-tumor drugs, anti-tussives, anti-uricemic drugs, amino-acid preparations, antiemetics, antiobesity drugs, antiparasitics, antipyretics, appetite stimulants, cerebral dilators, chelating agents, cholecystokinin antagonists, cognition activators, deodorants, dermatological agents, diabetes agents, diuretics, erythropoietic drugs, fertility agents, synthetic hormones, laxatives, mineral supplements, neuroleptics, neuromuscular agents, peripheral vaso-dilators, prostaglandins, vaginal preparations, vaso-constrictors and vertigo agents.

The bio-effecting agent is selected from the group consisting of acetaminophen, acetic acid, acetylsalicylic acid, buffered acetylsalicylic acid, albuterol, albuterol sulfate, ethanol isopropanol, allantoin, aloe, aluminum acetate, aluminum carbonate, aluminum chlorohydrate, aluminum hydroxide, alprozolam, amino acids, aminobenzoic acid, amoxicillin, ampicillin, amsacrine, amsalog, anethole, aspartame, atenolol, bacitracin, balsam peru, beclomethasone dipropionate, benzocaine, benzoic acid, benzophenones, benzoyl peroxide, biotin, bisacodyl, bornyl acetate, bromopheniramine maleate, buspirone, caffeine, calamine, calcium, calcium carbonate, calcium casinate, calcium hydroxide, camphor, captopril, cascara sagrada, castor oil, Cephalosporins, cefaclor, cefadroxil, cephalexin, cetylalcohol, cetylpyridinium chloride, chelated minerals, chloramphenicol, chlorcyclizine hydrochloride, chlorhexidine gluconate, chloroxylenol, chloropentostatin, chlorpheniramine maleate, cholestyramine resin, choline bitartrate, cimetidine hydrochloride, cinnamedrine hydrochloride, citalopram, citric acid, Clenbuterol, cocoa butter, cod liver oil, codeine and codeine phosphate, clonidine, clonidine hydrochloride, clorfibrate, ciprofloxacin HCl, cyanocobalamin, cyclizine hydrochloride, DMSO, danthron, Dantrium, dexamethazone, dexbrompheniramine maleate, dextromethorphan hydrobromide, diazapam, dibucaine, diclofenac sodium, digoxin, diltiazem, dimethicone, dioxybenzone, diphenbydramine citrate,

diphenhydramine hydrochloride, docusate calicum, docusate potassium, docusate sodium, doxycycline hyclate, doxylamine succinate, efaroxan, enalapril, enoxacin, erythromycin, estropipate, ethinyl estradiol, ephedrine, epinephrine bitartrate, erythropoietin, eucalyptol, ferrous fumarate, ferrous gluconate, ferrous sulfate, folic acid, fosphenytoin, Flunixin Meglumine, fluoxetine HCl, furosemide, gabapentan, gentamicin, Gentocin sulfate, gemfibrozil, glipizide, glycerin, glyceryl stearate, griseofulvin, guaifenesin, hexyiresorcinol, hydrochlorothiaxide, hydrocodone bitartrate, hydrocortisone, hydrocortisone acetate, 8-hydroxyquinoline sulfate, ibuprofen, indomethacin, inositol, insulin, iodine, ipecac, iron, isoxicam, ketamine, Ketofin, koalin, lactic acid, lanolin, lecithin, lidocaine, lidocaine hydrochloride, lisinopril, liotrix, lovastatin, MSM (methylsulfonylmethane), magnesium carbonate, magnesium hydroxide, magnesium salicylate, magnesium trisilocate, mefenamic acid, meclofenanic acid, meclofenamate sodium, medroxyprogesterone acetate, methenam me mandelate, Methocarbamol, menthol, meperidine hydrochloride, metaproterenol sulfate, methyl nicotinate, methyl salicylate, methylcellulose, methsuximide, metromidazole, metromidazole hydrochloride, metoprolol tartrate, miconazole nitrate, mineral oil, minoxidil, morphine, naproxen, naproxen sodium, nifedipine, neomycin sulfate, Neomycin-Bacitracin, niacin, niacinamide, nicotine, nicotinamide, nitroglycerin, nonoxynol-9, norethindone, norethindone acetate, nystatin, octoxynol, octyl dimethyl PABA, octyl methoxycinnamate, omega-3 polyunsaturated fatty acids, omeprazole, oxolinic acid, oxybenzone, oxtriphylline, para-aminobenzoic acid (PABA), padimate 0, paramethadione, Penicillin, pentastatin, peppermint oil, pentaerythriol tetranitrate, pentobarbital sodium, pheniramine maleate, phenobarbital, phenol, phenolphthalein, phenylbutazone, phenylephrine hydrochloride, phenylpropanolamine, phenylpropanolamine hydrochloride, phenytoin, phenelzine sulfate, pirmenol, piroxicam, polymycin B sulfate, potassium chloride, potassium nitrate, prazepam, prednisone, prednisolone, procainamide hydrochloride, procaterol, propoxyphene, propoxyphene HCl, propoxyphene napsylate, pramiracetin, pramoxine, pramoxine hydrochloride, propronolol HCl, pseudoephedrine hydrochloride, pseudoephedrine sulfate, pyridoxine, quinapril, quinidine gluconate, quinestrol, ralitoline, ranitadine, resorcinol, riboflavin, salicylic acid, sesame oil, shark liver oil. simethicone, sodium bicarbonate, sodium citrate, sodium fluoride, sodium monofluorophosphate, Sulfa-drugs, sulfanethoxazole, sulfur, tacrine, tacrine HCl, theophylline, terfenidine, thioperidone, trimetrexate, triazolam, timolol maleate, tretinoin, tetracycline hydrochloride, tolmetin, tolnaftate, triamcinilone, triclosan, triprolidine hydrochloride, undecylenic acid, vancomycin, verapamil HCl, vidaribine phosphate, vitamin A, vitamin B, vitamin C, vitamin D, vitamin B, vitamin K, witch hazel, xylometazoline hydrochloride, zinc, zinc sulfate, and zinc undecylenate.

The compositions of the invention can be made in paste form, gel forms, tablets and capsules. The paste form of the invention contains molasses in an amount effective to form a paste.

The gel forms of the invention are formed by mixing the actives with water and then adding a gelling agent. The gelling agent is selected from the group consisting of cellulose or a cellulose derivative in an amount of from 0.5 to 5 wt. % and said cellulose derivative is selected from the group consisting of hydroxypropyl methyl cellulose, hydroxymethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, cellulose acetate, ethyl cellulose, methyl hydroxy ethyl cellulose, hydroxy ethyl cellulose, cellulose gum carboxymethylcellulose and sodium carboxymethylcellulose.

In making the compositions of the invention, the active materials will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, methylcelluse, methyl and propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions may be formulated so as to provide rapid, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well-know in the art.

In a sixth embodiment of the invention, an animal feed is provided having chondroprotective and restorative properties. The animal feed base of the present invention comprises farinaceous material selected from the group consisting of wheat, wheat flour, wheat meal by-products and corn in an amount of 25 to 70% by weight based on the total weight of the feed, further comprising proteinaceous material selected from the group consisting of soybean meal, soy flour, peanut meal, cottonseed meal, safflower seed meal in an amount of from 5 to 40% by weight based on the total weight of the feed, further comprising fibrous material selected from the group consisting of soy hulls, cottonseed hulls, rice hulls in an amount of from about 2 to 35% by weight based on the total weight of the feed, further comprising nutritional supplements selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof, in an amount of from 3 to 4% by weight based on the total weight of the feed, further comprising a vegetable oil coating, said oil selected from the group consisting of soybean oil, corn oil, safflower oil, cottonseed oil, peanut oil, in an amount of from 1 to 15% by weight based on the total weight of the feed.

The above feed base is blended with a paste having the following formulation ranges: (a) 0.01–10 wt % hyaluronic acid or its pharmaceutical acceptable salts; (b) optionally 20–60 wt % glucosamine or its pharmaceutically acceptable salts; (c) optionally 1–15 wt % chondroitin or its pharmaceutical acceptable salts; (d) optionally nutritionally effective (recommended daily allowance) amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, B complex, B12, B1, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof; (e) optionally effective amounts of a

bioactive agent or drug; and (f) 15–35 wt % molasses. The feed of course is formulated in way to provide optimum nutrition and optimum chondroprotection depending on the specific animal and their current state of health.

The present invention is the most unique chondoprotective/restorative agent available. The molasses flavored oral paste provides a practical, efficient, and effective means of administration orally or top dressing feed. When added to the feed, the molasses base binds to the feed to insure total consumption. When necessary, an easy measurable dose can be administered orally. The highly palatable formulation of the invention is the first to combine high levels of Glucosamine sulfate (GS) with Chondroitin sulfate (CS) and Hyaluronic Acid (HA) in an easy to absorb, low molecular weight formula. It has also been shown that liquid or paste forms are more readily absorbed than encapsulated or powder forms. The chondroprotective/restorative agent of the invention enhance chondrocyte synthesis, increase synthesis of hyaluronic acid, inhibit enzymes that degrade cartilage, and reduce pain and synovitis. It must also slow down or reverse progression of the disease. The present invention, with its unique combination of GS, CS, and HA is the closest yet to satisfying these criteria.

These three substances are the three connective tissue molecules needed to rebuild and synthesize new tissue. Connective tissue is comprised mainly of collagen and proteoglycans. Proteoglycans provide the framework for collagen and hold water, enhancing the flexibility and resistance to compression needed to counteract physical stress. The building blocks for all proteoglycans are amino sugars. Glucosamine is the building block needed as the precursor for all subsequent amino sugar synthesis. The formation of N-acetylglucosamine, chondroitin sulfate, and hyaluronic acid require glucosamine for their synthesis. In fact, glucosamine makes up 50% of the hyaluronic acid molecule.

Glucosamine sulfate along with Chondroitin sulfate have become very popular supplements administered in the treatment of degenerative joint disease. Recent studies have questioned whether the combination produces better results than Glucosamine sulfate alone. Also there is much debate over which glucosamine salt is preferred. Embodiments of the present invention utilize Glucosamine sulfate as its source of Glucosamine. Most of the past and present research has been performed on the sulfated form. There is evidence that suggests that a component of the activity of GS and CS is related to the sulfate residues found in these compounds. Sulfur is an essential nutrient for the stabilization of the connective tissue matrix. It has been proposed that the sulfate molecules of GS and CS contribute to the therapeutic benefits of the compounds in degenerative joint disease. If this is true, it would suggest that GS, as opposed to N-acetylglucosamine and glucosamine HCl, is the best form of glucosamine supplementation. Recently, it has been shown that high-dose glucosamine may provide rapid symptomatic benefit and in the long term repair of damaged cartilage. The high dose of glucosamine not only promotes synthesis of cartilage proteogycans, but stimulates synovial production of hyaluronic acid. This would explain the anecdotal reports that a high dose of glucosamine is beneficial.

As previously explained, the present invention comprises a highly palatable formulation, which is the first to combine high levels of Glucosamine sulfate (GS) with Chondroitin sulfate (CS) and Hyaluronic Acid (HA) in an easy to absorb, low molecular weight formula.

Glucosamine, which is formed in the body as glucosamine 6-phosphate is the most fundamental building block required for the biosynthesis of the classes of compounds such as glucolipids, glycoproteins, glycosamineglycans, hyaluronate, and proteoglycans. Directly or indirectly, glucosamine plays a role in the formation of articular surfaces, tendons, ligaments, synovial fluid, skin, bone, heart valves, blood vessels and mucus secretions of the digestive, respiratory and urinary tracts. Glucosamine sulfate is greater than 90% absorbed and is quickly incorporated into articular cartilage following oral administration.

In one study, no LD50 was established for Glucosamine sulfate since even at very high levels (5000 mg/kg orally) there was no mortality in mice and rats. While treatment with GS does not produce the initial dramatic reductions in pain normally associated with NSAIDs, its ability to reduce pain is consistent and progressive throughout the course of it's administration, resulting in a long-term improvement in the condition. Glucosamine is a small molecule and is very soluble in water.

Chondroitin Sulfate achieves benefits much more slowly than glucosamine. Chondroitin bioavailability following oral administration is around 15%. Because of its lower bioavailability, the time needed to see a clinical response is lengthened. Chondroitin improves joint fluidity by drawing water to the cartilage tissue. When this water is drawn into the cartilage, it is accompanied by nutrients which are supplied to the cartilage. Additionally Chondroitin helps fight enzymes that inhibit transportation of nutrients into these tissues as it prevents other enzymes from tearing down cartilage tissue. Furthermore, Chondroitin, like Glucosamine, promotes the product of key cartilage components such as proteoglycans and it also prevents abnormal cell death.

Hyaluronic acid is one of many glycosaminoglycans of physiological significance. Other are Chondroitin sulfate, Heparin sulfate, and Dermatan sulfate. The HA molecule is very similar to that of Chondroitin sulfate. In numerous studies, the oral absorption of CS, HS and DS have been well documented. The bioavailabilities range from 15–20%. Hyaluronic acid has been shown to be absorbed through skin and reach the dermal lymphatics. Also, high levels of hyaluronan has been detected in the intestinal lymphatics. In addition, studies have been performed to determine the effects of HA secreted in saliva. Others have looked at hyaluronic acid production by oral epithelial cells. According to the present invention, there is a beneficial effect when Glucosamine sulfate, Chondroitin sulfate, and Hyaluronic acid are administered orally. Generally, the oral administration of a gel or paste form composition of HA, GS, and CS has a quicker clinical response than is produced when each component of the composition is given individually. A significant difference is an acute or a rapid relief from joint pain, inflammation and swelling achieved by oral administration of the composition. A dramatic improvement over seven to ten days is achieved with the present embodiment, whereas it usually takes weeks for that effect to occur when GS and CS are administered without HA. Another beneficial embodiment is an oral preparation for oral administration of an effective chondroprotective/restorative amount of HA to, for example, an equine. The administration of the HA composition orally and having a clinical effect eliminates more invasive procedures. Other ways to give HA would be more invasive, such an injection by IV or other administration into the joints. Thus, the embodiments of the present invention include oral preparations that are administrable by less invasive routes and which also may provide the sole clinically effective way to orally administer HA when other routes (e.g., injection) are not possible.

Another benefit is that embodiments of the present invention, with its high dose of Glucosamine sulfate, Hyaluronic acid, and Chondroitin sulfate, appears to have a synergistic effect which hastens the clinical response.

One further embodiment of the present invention is a unique formulation that combines Glucosamine sulfate, Chondroitin sulfate, and Hyaluronic acid into a paste formulation for direct oral administration or top dressing feed. This is the only product available which combines these three substances which are critical for cartilage metabolism and production of synovial fluid. Also, this embodiment is the only oral paste formulation available for any one of these supplements. Early clinical trials have shown that when the three products are combined, they have a synergistic effect. The clinical effects have been impressive. Data has shown a quicker clinical response when GS, CS, and HA are combined than when they are used individually. Conditions in which embodiments of the present invention would be beneficial:

1) Osteoarthritis
2) Joint effusion
3) Joint inflammation and pain
4) Post operative arthroscopic surgery
5) Restoring proper joint function
6) Promote metabolic activity of chondrocytes (cartilage producing cells)
7) Inhibit enzymes that degrade cartilage
8) Stimulate the production of Hyaluronic acid.

Embodiments of the present invention possess the following advantages:

1) Only paste formulation
2) Only combination of GS, CS, HA in a paste formulation
3) Only oral paste form of Glucosamine
4) Only oral paste form of Chondroitin
5) Only oral paste form of Hyaluronic acid
6) Only oral paste in a molasses flavored base
7) Only oral gel in apple flavored carboxymethylcellulose base.

One embodiment of the present invention possesses a molasses flavor. Other flavors would include apple, cherry, and any other palatable flavor.

One embodiment of the present invention comprises the following:

	Wt %
Glucosamine sulfate	46.03
Chondroitin sulfate	4.60
Sodium Hyaluronate	0.18
Manganese sulfate	0.18
Powdered sugar	8.70
Xanthan gum	0.10
Molasses	25.00
Water	14.00
Glycerine	0.70
Corn Starch	0.30
Sodium Benzoate	0.50

Embodiments of the present invention in a paste formulation has many advantages. When adding to feed, the formulation will stick to grain to insure total consumption. Embodiments of the paste formulation can be given orally (direct administration) or added to feed—depending on management of animals (e.g., whether turned out in field vs. stall confinement). Other advantages include the following:

1) Better absorption with liquids
2) Molasses flavored paste—more palatable
3) Apple flavored gel—more palatable
4) Sticky consistency—animal cannot spit product from mouth which insures total dose
5) Syringe dose insures more accurate dose.
6) Brown sugar included—more palatable

Effects of GS vs CS:

Glucosamine Sulfate:

1) Enhances chondrocyte synthesis
2) Enhances synthesis of hyaluronic acid
3) Reduces joint pain
4) Reduces synovitis

Chondroitin Sulfate:

1) Also helps with chondrocyte synthesis
2) CS has been found to inhibit degradative enzymes in cartilage
3) CS strengthens and enhances vessels that feed joints or supply them with nutrients by reducing arterial plaque and clear cholesterol deposits.
4) Reduces joint pain and improves joint mobility.
5) Reduces synovitis associated with joint arthritis.

Neither GS or CS fulfills the quest for the ideal chondroprotective/restorative agent separately but when combined they appear to provide the necessary components for the health and wellbeing of the joint. Hyaluronic acid complements the combination by helping to restore the HA levels needed for joint health and lubrication which are decreased when synovitis is present.

Hyaluronic acid is a glycosaminoglycan. Other glycosaminoglycans are Chondroitin sulfate, Heparin sulfate, and Dermatan sulfate. The most abundant GAG is Chondroitin sulfate. The three related GAGs have been found to be absorbed orally. Because of their chemical similarities and the clinical reports of improvement of synovitis, HA has a synergistic effect with GS and CS when given orally. This effect is observed as a more rapid clinical response than when GS and CS are given individually.

Clinically, responses are seen in 7 to 10 days vs three to four weeks or not at all when GS and CS are given without HA. Therefore, we have seen a dramatic decrease in synovitis when HA is combined with GS and CS. This leads us to conclude that HA is absorbed orally and effective either alone or in combination with GS and CS. Therefore, an additional embodiment of the invention comprises a composition including HA and any acceptable carrier, such as the paste formulation disclosed herein and any other liquid, powder, gel or similar type carrier.

Another embodiment of the invention includes a paste formulation containing the active component isoxuprine. Isoxuprine is a vasodilator and is utilized in treatment of many afflictions including the treatment of navicular disease. One effect of isoxuprine is that it stimulates the vasodilator nerves, such as the vaso-inhibitory and vasohypotonic nerves, and causes dilation or relaxation of the blood vessels. Administration of isoxuprine to a patient, such as an animal, in the form of a paste is beneficial to ensure adequate administration.

The present invention is illustrated by the following Examples, but should not be construed to be limited thereto. In the Examples, "part" and "%" are all part by weight or % by weight unless specified otherwise. Examples 1–14 are paste compositions of the invention.

EXAMPLE 1

Component	Wt %
Sodium Hyaluronate	0.144
Powdered Sugar 10X	60.144
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

EXAMPLE 2

Component	Wt %
Chondroitin Sulfate	4
Sodium Hyaluronate	0.144
Powdered Sugar 10X	50.144
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	29.5
Water DI	14.4
TOTAL	100

EXAMPLE 3

Component	Wt %
Glucosamine Sulfate	40.144
Sodium Hyaluronate	0.144
Powdered Sugar 10X	20
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

EXAMPLE 4

Component	Wt %
Glucosamine Sulfate	36.144
Chondroitin Sulfate	4
Sodium Hyaluronate	0.144
Powdered Sugar 10X	20
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

EXAMPLE 5

Component	Wt %
Glucosamine Sulfate	36
Sodium Hyaluronate	0.144
Manganese Sulfate	0.144
Powdered Sugar 10X	24
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

-continued

EXAMPLE 6

Component	Wt %
Chondroitin Sulfate	4
Sodium Hyaluronate	0.144
Manganese Sulfate	0.144
Powdered Sugar 10X	56
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

EXAMPLE 7

Component	Wt %
Glucosamine Sulfate	36
Chondroitin Sulfate	4
Sodium Hyaluronate	0.144
Manganese Sulfate	0.144
Powdered Sugar 10X	20
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

EXAMPLE 8

Component	Wt %
Glucosamine Sulfate	35
Chondroitin Sulfate	4
Sodium Hyaluronate	0.144
Manganese Sulfate	0.144
Vitamin C	3
Powdered Sugar 10X	20
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

EXAMPLE 9

Component	Wt %
Glucosamine Sulfate	36
Chondroitin Sulfate	4
Sodium Hyaluronate	0.144
Manganese Sulfate	0.144
Vitamin D	200 IU
Powdered Sugar 10X	20
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

-continued

EXAMPLE 10

Component	Wt %
Glucosamine Sulfate	36
Chondroitin Sulfate	4
Sodium Hyaluronate	0.144
Manganese Sulfate	0.144
Ibuprofen	200 mg
Powdered Sugar 10X	20
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

EXAMPLE 11

Component	Wt %
Glucosamine Sulfate	36
Chondroitin Sulfate	4
Sodium Hyaluronate	0.144
Manganese Sulfate	0.144
Erythromycin	200 mg
Powdered Sugar 10X	20
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

EXAMPLE 12

Component	Wt %
Glucosamine Sulfate	36
Chondroitin Sulfate	4
Sodium Hyaluronate	0.144
Manganese Sulfate	0.144
Isoniprine	100 mg
Powdered Sugar 10X	20
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

EXAMPLE 13

Component	Wt %
Glucosamine Sulfate	40.144
Sodium Hyaluronate	0.144
Ibuprofen	800 mg
Powdered Sugar 10X	20
Glycerine	0.7
Xanthan Gum	0.2
Sodium Benzoate	0.7
Citric Acid Anhydrous	0.2
Molasses	23.5
Water DI	14.4
TOTAL	100

-continued

EXAMPLE 14

Component	Wt %
Glucosamine Sulfate	46.03
Chondroitin Sulfate	4.60
Sodium Hyaluronate	0.38
Manganese Sulfate	0.18
Powdered Sugar 10X	8.70
Glycerine	0.7
Xanthan Gum	0.10
Sodium Benzoate	0.50
Corn Starch	0.30
Molasses	25.00
Water DI	14.0
TOTAL	100

EXAMPLE 15

The following Example is directed to a gel of HA using CMC as the gelling agent.

Component	Wt %
Sodium Hyaluronate	1.00
Sodium Carboxymethyl cellulose	1.00
Propylene glycol	1.20
Sodium Benzoate	0.50
Citric Acid	0.30
Apple Flavor	1.5
Water DI	94.5
TOTAL	100

EXAMPLE 16

The following Example is directed to a gel of HA and chondroitin sulphate using CMC as the gelling agent.

Component	Wt %
Sodium Hyaluronate	1.00
Chondroitin Sulphate	4.00
Sodium Carboxymethyl cellulose	1.00
Propylene glycol	1.20
Sodium Benzoate	0.50
Citric Acid	0.30
Apple Flavor	1.5
Water DI	90.5
TOTAL	100

EXAMPLE 16

Hard gelatin capsules are prepared using the following ingredients

Component	Amount mg
Sodium Hyaluronate	100.00
Starch dried	200.00
Magnesium stearate	10.00
TOTAL	310.00

EXAMPLE 17

Hard gelatin capsules are prepared using the following ingredients

Component	Amount mg
Sodium Hyaluronate	100.00
Chondroitin sulphate	200.00
Starch dried	200.00
Magnesium stearate	10.00
TOTAL	510.00

The above ingredients are mixed and filled into hard gelatin capsules in 510 mg quantities.

EXAMPLE 18

Hard gelatin capsules are prepared using the following ingredients

Component	Amount mg
Sodium Hyaluronate	100.00
Microcrystalline cellulose	400.00
Silicon Dioxide, fumed	10.00
Stearic Acid	5.00
TOTAL	310.00

The components are blended and compressed to form tablets each weighing 665 mg.

While the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications, and variations will be apparent to those skilled in the art in light of the foregoing description. Accordingly, it is intended to embrace all such alternatives, modifications, and variations which fall within the spirit and broad scope of the invention.

I claim:

1. An orally administrable Chondroprotective/Restorative composition in gel or paste form for administration to a mammal comprising an effective amount Hyaluronic Acid or its pharmaceutically acceptable salts an a pharmaceutically acceptable gelling or pasting agent capable of forming a gel or a paste selected from the group consisting of hydroxypropyl methyl cellulose, hydroxymethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, cellulose acetate, ethyl cellulose, methyl hydroxy ethyl cellulose, hydroxy ethyl cellulose, cellulose gum carboxymethylcellulose, sodium carboxymethylcellulose and molasses.

2. The Chondroprotective/Restorative composition of claim 1 further including nutritionally effective amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof.

3. An orally administrable Chondroprotective/Restorative composition comprising:

(a) an effective amount of Glucosamine sulfate;

(b) an effective amount Hyaluronic Acid or pharmaceutically acceptable salts thereof; and

(c) a pharmaceutically acceptable gelling or pasting agent capable of forming a gel or a paste selected from the group consisting of hydroxypropyl methyl cellulose, hydroxymethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, cellulose acetate, ethyl cellulose, methyl hydroxy ethyl cellulose, hydroxy ethyl cellulose, cellulose gum carboxymethylcellulose, sodium carboxymethylcellulose and molasses.

4. The Chondroprotective/Restorative composition of claim 3 further including nutritionally effective amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof.

5. An orally administrable Chondroprotective/Restorative composition comprising

(a) an effective amount of Chondroitin sulfate;

(b) an effective amount of Hyaluronic Acid or pharmaceutically acceptable salts thereof; and

(c) a pharmaceutically acceptable gelling or pasting agent capable of forming a gel or a paste selected from the group consisting of hydroxypropyl methyl cellulose, hydroxymethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, cellulose acetate, ethyl cellulose, methyl hydroxy ethyl cellulose, hydroxy ethyl cellulose, cellulose gum carboxymethylcellulose, sodium carboxymethylcellulose and molasses.

6. The Chondroprotective/Restorative composition of claim 5 further including nutritionally effective amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof.

7. An orally administrable Chondroprotective/Restorative composition comprising

(a) an effective amount of Glucosamine sulfate;

(b) an effective amount of Chondroitin sulfate;

(c) an effective amount of Hyaluronic Acid or pharmaceutically acceptable salts thereof; and

(d) a pharmaceutically acceptable gelling or pasting agent capable of forming a gel or a paste selected from the group consisting of hydroxypropyl methyl cellulose, hydroxymethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, cellulose acetate, ethyl cellulose, methyl hydroxy ethyl cellulose, hydroxy ethyl cellulose, cellulose gum carboxymethylcellulose, sodium carboxymethylcellulose and molasses.

8. The Chondroprotective/Restorative composition of claim 7 further including nutritionally effective amounts of

a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl copper, iron, manganese, iodine, zinc and combinations thereof.

9. A therapeutic and Chondroprotective/Restorative composition in gel form for oral administration comprising:

(a) an effective amount of hyaluronic Hyaluronic Acid or its pharmaceutically acceptable salts;

(b) an effective amount of a therapeutic drug; and

(c) a pharmaceutically acceptable gelling or pasting agent capable of forming a gel or a paste selected from the group consisting of hydroxypropyl methyl cellulose, hydroxymethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, cellulose acetate, ethyl cellulose, methyl hydroxy ethyl cellulose, hydroxy ethyl cellulose, cellulose gum carboxymethylcellulose, sodium carboxymethylcellulose and molasses.

10. The therapeutic and Chondroprotective/Restorative composition of claim 9 wherein said therapeutic drug is selected from the group consisting of acetaminophen, acetic acid, acetylsalicylic acid, buffered acetylsalicylic acid, albuterol, albuterol sulfate, ethanol isopropanol, allantoin, aloe, aluminum acetate, aluminum carbonate, aluminum chlorohydrate, aluminum hydroxide, alprozolam, amino acids, aminobenzoic acid, amoxicillin, ampicillin, amsacrine, amsalog, anethole, aspartame, atenolol, bacitracin, balsam peru, beclomethasone dipropionate, benzocaine, benzoic acid, benzophenones, benzoyl peroxide, biotin, bisacodyl, bornyl acetate, brompheniramine maleate, buspirone, caffeine, calamine, calcium, calcium carbonate, calcium casinate, calcium hydroxide, camphor, captopril, cascara sagrada, castor oil, Cephalosporins, cefaclor, cefadroxil, cephalexin, cetylalcohol, cetylpyridinium chloride, chelated minerals, chloramphenicol, chlorcyclizine hydrochloride chlorhexidine gluconate, chloroxylenol, chloropentostatin, chlorpheniramine maleate, cholestyramine resin, choline bitartrate, cimetidine hydrochloride, cinnamedrine hydrochloride, citalopram, citric acid, Clenbuterol, cocoa butter, cod liver oil, codeine and codeine phosphate, clonidine, clonidine hydrochloride, clorfibrate, ciprofloxacin HCl, cyanocobalamin, cyclizine hydrochloride, DMSO, danthron, Dantrium, dexamethazone, dexbrompheniranime maleate, dextromethorphan hydrobromide, diazapam, dibucaine, diclofenac sodium, digoxin, diltiazem, dimethicone, dioxybenzone, diphenhydramine citrate, diphenhydramine hydrochloride, docusate calicum, docusate potassium, docusate sodium, doxycycline hyclate, doxylamine succinate, efaroxan, enalapril, enoxacin, erythromycin, estropipate, ethinyl estradiol, ephedrine, epinephrine bitartrate, erythropoietin, eucalyptol, ferrous fumarate, ferrous gluconate, ferrous sulfate, folic acid, fosphenytoin, Flunixin Meglumine, fluoxetine HCl, furosemide, gabapentan, gentamicin, Gentocin sulfate, gemfibrozil, glipizide, glycerin, glyceryl stearate, griseofulvin, guaifenesin, hexylresorcinol, hydrochlorothiaxide, hydrocodone bitartrate, hydrocortisone, hydrocortisone acetate, 8-hydroxyquinoline sulfate, ibuprofen, indomethacin, inositol, insulin, iodine, ipecac, iron, isoxicam, Isoxuprine, ketamine, Ketofin, koalin, lactic acid, lanolin, lecithin, lidocaine, lidocaine hydrochloride, lifinopril, liotrix, lovastatin, MSM (methylsulfonylmethane), magnesium carbonate, magnesium hydroxide, magnesium salicylate, magnesium trisilocate, mefenamic acid, meclofenanic acid, meclofenamate sodium, medroxyprogesterone acetate, methenamine, mandelate, Methocarbamol, menthol, meperidine hydrochloride, metaproterenol sulfato, methyl nicotinate, methyl salicylate, methylcellulose, methsuximide, metromidazole, metromidazole hydrochloride, metoprolol tartrate, miconazole nitrate, mineral oil, minoxidil, morphine, naproxen, naproxen sodium, nifedipine, neomycin sulfate, Neomycin-Bacitracin, niacin, niacinamide, nicotine, nicotinamide, nitroglycerin, nonoxynol-9, norethindone, norethindone acetate, nystatin, octoxynol, octyl dimethyl PABA, octyl methoxycinnamate, omega-3 polyunsaturated fatty acids, omeprazole, oxolinic acid, oxybenzone, oxtriphylline, para-aminobenzoic acid (PABA), padimate O, paramethadione, Penicillin, pentastatin, peppermint oil, pentaerythriol tetranitrate, pentobarbital sodium, pheniramine maleate, phenobarbital, phenol, phenolphthalein, phenybutazone phenylbutazone, phenylephrine hydrochloride, phenylpropanolamine, phenylpropanolamine hydrochloride, phenytoin, phenelzine sulfate, pinnenol, piroxicam, polymycin B sulfate, potassium chloride, potassium nitrate, prazepam, prednisone, prednisolone, procainamide hydrochloride, procaterol, propoxyphene, propoxyphene HCl, propoxyphene napsylate, pramiracetin, pramoxine, pramoxine hydrochloride, propronolol HCl pseudoephedrine hydrochloride, pseudoephedrine sulfate, pyridoxine, quinapril, quinidine gluconate, quinestrol, ralitoline, ranitadine, resorcinol, riboflavin, salicylic acid, sesame oil, shark liver oil, simethicone, sodium bicarbonate, sodium citrate, sodium fluoride, sodium monofluorophosphate, Sulfa-drugs, sulfanethoxazole, sulfur, tacrine, tacrine HCl, theophylline, terfenidine, thioperidone, trimetrexate, triazolam, timolol maleate, tretinoin, tetracycline hydrochloride, tolmetin, tolnaftate, triamcinolone, triclosan, triprolidine hydrochloride, undecylenic acid, vancomycin, verapamil HCl, vidaribine phosphate, vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, vitamin K, witch hazel, xylometazoline hydrochloride zinc, zinc sulfate, and zinc undecylenate.

11. An oral Chondroprotective/Restorative composition in paste from comprising:

(a) an effective amount of Hyaluronic Acid or its pharmaceutically acceptable salts; and

(b) a sufficient amount of molasses to make a paste.

12. The Chondroprotective/Restorative composition of claim 11 further including glucosamine sulfate.

13. The Chondroprotective/Restorative composition of claim 12 further including nutritionally effective amounts of vitamins and minerals.

14. The Chondroprotective/Restorative of claim 11 further including chondroitin sulfate.

15. An orally administrable Chondroprotective/Restorative composition in gel form comprising:

(a) an effective amount of Hyaluronic Acid or its pharmaceutically acceptable salts;

(b) water; and

(c) a sufficient amount of carboxymethylcellulose or its sodium salt to make a gel.

16. The Chondroprotective/Restorative composition of claim 15 further including glucosamine sulfate.

17. The Chondroprotective/Restorative composition of claim 15 further including chondroitin sulfate.

18. The chondroprotective/Restorative composition of claim 15 further including nutritionally effective amounts of vitamins and minerals.

19. The Chondroprotective/Restorative composition of claim 18 further including chondroitin sulfate.

20. A method of treating osteoarthritis, joint effusion, joint inflammation and pain, synovitis, lameness, post operative arthroscopic surgery, deterioration of proper joint function, the reduction or inhibition of metabolic activity of chondrocytes, the activity of enzymes that degrade cartilage, the reduction or inhibition of the production of Hyaluronic acid in a mammal, said method comprising orally administering to said mammal a therapeutically effective amount of the composition of claim 1.

21. The method of claim 20 further including an effective amount of Glucosamine or its pharmaceutically acceptable salts.

22. The method of claim 21 wherein said pharmaceutically acceptable salt is glucosamine sulfate.

23. The method of claim 20 further including an effective amount of chondroitin or its pharmaceutically acceptable salts.

24. The method of claim 23 wherein said pharmaceutically acceptable salt is chondroitin sulfate.

25. The method of claim 20 further including therapeutically effective amounts of glucosamine sulfate and chondroitin sulfate.

26. The method according to claim 20 wherein said hyaluronic acid is uncrosslinked.

27. The method according to claim 26 wherein said therapeutically effective amount of sodium hyaluronate is in the range of 10 mg to 2000 mg.

28. The method according to claim 20 wherein said pharmaceutically acceptable salt is sodium hyaluronate.

* * * * *